UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2019

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from ________to ________
Commission File Number 001-38537

AVROBIO, INC.
(Exact name of registrant as specified in its charter)

Delaware **(State or other jurisdiction of incorporation or organization)**	**81-0710585** **(I.R.S. Employer Identification No.)**
One Kendall Square **Building 300, Suite 201** **Cambridge, Massachusetts** **(Address of principal executive offices)**	**02139** **(Zip Code)**

(617) 914-8420
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	AVRO	Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Act:
None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer", "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐	Smaller reporting company	☒
		Emerging growth company	☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately $289,225,075 as of June 28, 2019 (based on a closing price of $16.26 share as quoted by the Nasdaq Global Select Market as of such date). In determining the market value of non-affiliate common stock, shares of the registrant's common stock beneficially owned by officers, directors and affiliates have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The registrant had 36,030,495 shares of Common Stock, $0.0001 par value per share, outstanding as of March 6, 2020.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates by reference certain information from the registrant's definitive Proxy Statement for its 2020 annual meeting of shareholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2019. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K.

AVROBIO, Inc.
Annual Report on Form 10-K for the Fiscal Year Ended December 31, 2019
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Forward-looking Information

This Annual Report on Form 10-K contains forward-looking statements which are made pursuant to the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements may be identified by such forward-looking terminology as “aims,” “anticipates,” “believes,” “continue,” “could,” “designed to,” “estimates,” “expects,” “intends,” “may,” “plans,” “potential,” “predicts,” “strives,” “should,” or the negative of these terms or other comparable terminology. Our forward-looking statements are based on a series of expectations, assumptions, estimates and projections about our company, are not guarantees of future results or performance and involve substantial risks and uncertainty. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements. Our business and our forward-looking statements involve substantial known and unknown risks and uncertainties, including the risks and uncertainties inherent in our statements regarding:

- the timing, progress and results of preclinical studies and clinical trials for our programs and product candidates, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available and our research and development programs;
- the existence or absence of side effects or other properties relating to our product candidates which could delay or prevent their regulatory approval, limit their commercial potential, or result in significant negative consequences following any potential marketing approval;
- the durability of effects from our product candidates;
- the timing, scope or likelihood of regulatory filings and approvals;
- our ability to develop and advance product candidates into, and successfully complete, clinical studies;
- our expectations regarding the size of the patient populations for our product candidates, if approved for commercial use;
- the implementation of our business model and our strategic plans for our business, product candidates, technology and plato™ platform, including our transition to and expected benefits of a proprietary four-plasmid-produced lentiviral vector and our use of a therapeutic drug monitoring conditioning regimen with busulfan;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of our product candidates, if approved;
- the scalability and commercial viability of our manufacturing methods and processes, including our move to a closed, automated system;
- the rate and degree of market acceptance and clinical utility of our product candidates, in particular, and gene therapy, in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- our competitive position;
- the scope of protection we and/or our licensors are able to establish and maintain for intellectual property rights covering our current and future product candidates, as well as any statements as to whether we do or do not infringe, misappropriate or otherwise violate any third-party intellectual property rights;
- our financial performance;
- our ability to retain the continued service of our key professionals and to identify, hire and retain additional qualified professionals;
- developments and projections relating to our competitors and our industry;
- our expectations related to the use of our cash reserves;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to remediate the material weaknesses that we and our independent registered public accounting firm previously identified and avoid any findings of material weaknesses or significant deficiencies in the future;
- the impact of laws and regulations, including without limitation recently enacted tax reform legislation;
- our expectations regarding the time during which we are an emerging growth company under the JOBS Act; and
- other risks and uncertainties, including those listed under the caption “Risk Factors.”

All of our forward-looking statements are as of the date of this Annual Report on Form 10-K only. In each case, actual results may differ materially from such forward-looking information. We can give no assurance that such expectations or forward-looking statements will prove to be correct. An occurrence of or any material adverse change in one or more of the risk factors or risks and uncertainties referred to in this Annual Report on Form 10-K or included in our other public disclosures or our other periodic reports or other documents or filings filed with or furnished to the Securities and Exchange Commission, or the SEC, could materially and adversely affect our business, prospects, financial condition and results of operations. Except as required by law, we do not undertake or plan to update or revise any such forward-looking statements to reflect actual results, changes in plans, assumptions, estimates or projections or other circumstances affecting such forward-looking statements occurring after the date of this Annual Report on Form 10-K, even if such results, changes or circumstances make it clear that any forward-looking information will not be realized. Any public statements or disclosures by us following this Annual Report on Form 10-K that modify or impact any of the forward-looking statements contained in this Annual Report on Form 10-K will be deemed to modify or supersede such statements in this Annual Report on Form 10-K.

PART I

Unless the context requires otherwise, references in this Annual Report on Form 10-K to the "Company," "AVROBIO," "we," "us," and "our" refer to AVROBIO, Inc. Our "board of directors" refers to the board of directors of AVROBIO, Inc.

Item 1. Business

Overview

We are a leading clinical-stage gene therapy company with a mission to free people from a lifetime of genetic disease. Our company is focused on developing potentially curative *ex vivo* lentiviral-based gene therapies to treat patients with rare diseases following a single dose treatment regimen. Our gene therapies employ hematopoietic stem cells that are harvested from the patient and then modified with a lentiviral vector to insert the equivalent of a functional copy of the gene that is defective in the target disease. We believe that our approach, which is designed to transform stem cells from patients into therapeutic products, has the potential to provide curative benefit for a range of diseases. Our initial focus is on a group of rare genetic diseases referred to as lysosomal diseases, some of which today are primarily managed with enzyme replacement therapies, or ERTs. These lysosomal diseases have well-understood biologies, identified patient populations, established standards of care yet with significant unmet needs, and represent large market opportunities with approximately $4.0 billion in worldwide net sales in 2019.

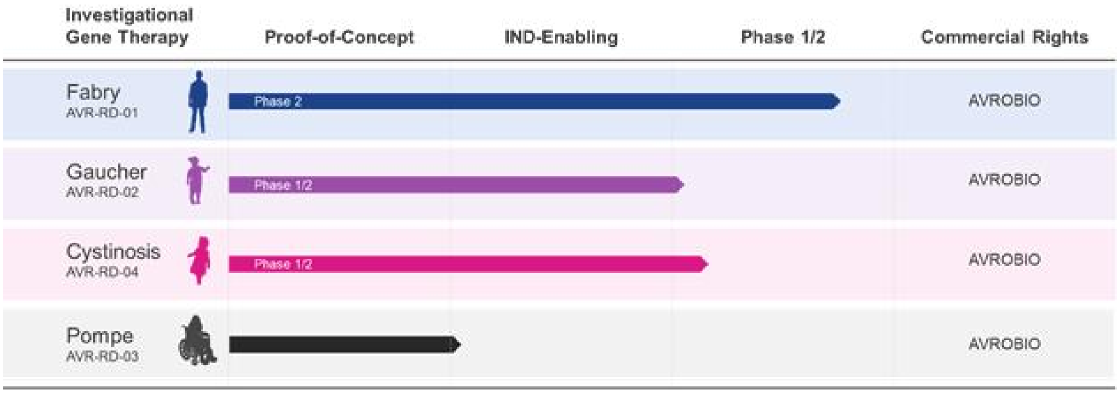
Our initial pipeline is comprised of four lentiviral-based gene therapy programs, including AVR-RD-01 for the treatment of Fabry disease, AVR-RD-04 for the treatment of cystinosis, AVR-RD-02 for the treatment of Gaucher disease and AVR-RD-03 for the treatment of Pompe disease. AVR-RD-01 is currently being evaluated in an investigator-sponsored Phase 1 clinical trial and a company-sponsored Phase 2 clinical trial. Five patients have been dosed in the investigator-sponsored Phase 1 clinical trial of AVR-RD-01, and enrollment is complete. As of March 6, 2020, four patients have been dosed in our company-sponsored Phase 2 clinical trial of AVR-RD-01, and we are actively recruiting additional potential patients for our currently active sites in Australia, Canada and the United States. AVR-RD-04 is currently being studied by our collaborators at the University of California, San Diego, or UCSD, in a Phase 1/2 investigator-sponsored clinical trial, and as of March 6, 2020 one patient has been dosed. In January 2020, we announced that we received notice of clearance from the U.S. Food and Drug Administration, or FDA, regarding an Investigational New Drug, or IND, application for AVR-RD-02, our investigational gene therapy for the treatment of Gaucher disease. The Phase 1/2 clinical trial for AVR-RD-02 is actively recruiting in Australia and Canada, with additional sites planned in the United States. Our AVR-RD-03 program for Pompe disease is currently in preclinical development with the first IND-enabling preclinical study initiated in 2019.

Since its first clinical use in 2003, lentiviral-based gene therapy has been observed to be well-tolerated in third parties' clinical trials for rare diseases such as transfusion-dependent beta thalassemia, cerebral adrenoleukodystrophy, or CALD, metachromatic leukodystrophy, or MLD, and adenosine deaminase severe combined immunodeficiency, or ADA-SCID. Initially, the use of *ex vivo* lentiviral-based gene therapies was restricted primarily to the most severe diseases where the risks of the typical requirement for ablating the patients' bone marrow had a clinically justifiable risk/benefit profile. To date, over 350 patients have been treated with lentiviral-based gene therapies in third parties' and our rare disease clinical trials, and we believe the technology can be developed for other serious conditions based on a rigorous risk/benefit assessment. The ablation procedure, also known as the conditioning regimen, is typically an essential step in the *ex vivo* gene therapy treatment procedure and is administered prior to the gene therapy. The higher the level of conditioning, the greater the potential risk of more serious complications, such as veno-occlusive disease. However, we believe the risk of more serious complications can be managed through utilization of therapeutic drug monitoring, or TDM, to enable careful titrating of exposure to the drug to a specific area under the curve, or AuC. The conditioning regimen utilized as part of our plato platform includes TDM to assess how rapidly the individual patient metabolizes the conditioning agent so physicians can adjust the dose as needed, with a goal of minimizing side effects while maximizing the potential of durable engraftment. Such an approach could potentially allow the conditioning regimen to be performed during a limited hospital stay or potentially through an outpatient procedure, on a case-by-case basis as may be directed by the patient's physician. We believe our approach, utilizing a single myeloablative conditioning agent, busulfan, coupled with TDM designed to titrate to a specific AuC, has the potential to extend the reach of our gene therapies to a broad range of diseases as first-line therapies. Our goal is to broaden the applicability of lentiviral-based gene therapy by initially targeting monogenic diseases with an identified gene, recognized biology and that could potentially benefit from the sustained systemic delivery of an active protein.

We are initially targeting rare lysosomal diseases in which the current standard of care provides the mechanistic proof that the enzymes or proteins produced endogenously following treatment with our gene therapies can offer benefit to patients. Typically, in lysosomal diseases, a gene mutation results in the deficiency or malfunctioning of an enzyme or other protein. This results in the inability of lysosomes to properly process cellular materials such as damaged organelles. As a result, substrates and their metabolites accumulate to toxic levels in the body's cells and, in turn, disrupt the function of multiple tissues and organs. Fabry disease, Gaucher disease and Pompe disease are currently primarily managed by bi-weekly, multi-hour infusions with ERTs that seek to exogenously replace the missing functional enzyme. However, given their pharmacokinetics, most ERTs typically remain in the plasma only for a short period of time and thus are not ideal because they are only dosed every two weeks. These existing therapies manage, rather than cure, the underlying diseases and, as a result, patients continue to have disease progression. Further, the frequent, periodic and life-long dosing schedule required for ERTs results in significant costs for the healthcare system and is burdensome for the patient.

We believe our gene therapies leverage the well-understood mechanism of ERTs by transforming a patient's own cells into a drug product that enables the patient to express functional enzyme or other protein and mirror the biology seen in an otherwise healthy individual. We believe that a single dose of our gene therapies may provide meaningful life-long benefit to these patients and potentially halt the progression of these diseases while also potentially providing significant health economic advantages.

Our programs leverage years of extensive preclinical and early clinical research by leading researchers, as well as our internal research and ongoing clinical efforts. The status of our initial lentiviral-based gene therapy programs is reflected below.



Our lead product candidate, AVR-RD-01 for the treatment of Fabry disease, is derived from hematopoietic stem cells to which the gene encoding plasma α-galactosidase A, or AGA, is added in an *ex vivo* process using a lentiviral vector. In July 2019, we reported that a kidney biopsy taken at 12 months post-treatment for the first patient in the Phase 2 trial showed an 87-percent reduction from baseline in the average number of globotriaosylceramide, or Gb3, inclusions per peritubular capillary. In addition, in February 2020 we reported data from the first three patients in the Phase 2 trial measured as of 18, 12 and nine months, respectively, indicating sustained increased leukocyte and plasma enzyme activity, suggesting that these patients are now producing an endogenous supply of AGA. For the first and third Phase 2 patients, data indicate that their decreased plasma lyso-globotriaosylsphingosine, or lyso-Gb3, levels, a key biomarker for monitoring Fabry disease, have been sustained below their baseline at 18 and six months after dosing, respectively. The second Phase 2 patient, a cardiac variant who does not have classic Fabry disease, did not show a decrease in plasma lyso-Gb3 levels, as expected. The fourth patient in the Phase 2 clinical trial was dosed in December 2019 with our plato platform. We have opened two U.S. sites for our ongoing Phase 2 clinical trial of AVR-RD-01 and are actively recruiting potential patients for our sites in Australia, Canada and the United States.

In an ongoing investigator-sponsored Phase 1 clinical trial of patients with Fabry disease, AVR-RD-01 has been observed to be well-tolerated and has led to the production of active AGA enzyme in all five patients, with data from the first patient exhibiting enzyme activity at 32 months after dosing. Four of the five patients in the Phase 1 clinical trial have had their plasma lyso-Gb3 levels reduced between 26 and 47 percent compared to their pre-treatment baseline levels. Data from the other patient in the trial, who discontinued ERT one month prior to receiving AVR-RD-01 and remains off ERT, through month six showed an initial decline and at month 12 showed a 23-percent increase in lyso-Gb3 levels, as compared to pre-treatment levels. This patient's lyso-Gb3 levels remain within the range for the Fabry disease patients on ERT observed in the Phase 1 clinical study.

In February 2020, we announced initial clinical data from the first patient dosed in the investigator-sponsored Phase 1/2 trial of AVR-RD-04, the investigational gene therapy for cystinosis. As of the safety data cut-off date of January 27, 2020, which was approximately three months following administration of the investigational gene therapy, there had been no reports of safety events attributed to the investigational drug product and no serious adverse events, or SAEs, had been reported. Three months following administration of AVR-RD-04, the first patient exhibited a vector copy number, or VCN, of 2.0. VCN, which is expressed as VCN per diploid genome, refers to the average number of copies of the lentiviral-vector inserted gene that are integrated into the genome of a cell and is a measure that can be used to help assess the durability of a gene therapy. Initial data on another biomarker -- the average granulocyte cystine level, which is one of the clinical trial's primary endpoints -- showed that the first patient's average granulocyte cystine level decreased from a baseline level of 7.8 nmol half cystine/mg protein to 1.5 nmol half cystine per milligram three months post-treatment with AVR-RD-04. The patient's baseline value was measured two weeks after discontinuation of cysteamine treatment, the current standard of care for cystinosis, and prior to initiating mobilization. As the Phase 1/2 clinical trial progresses, we expect to identify clinically meaningful measures, such as renal function, polyuria and crystal levels in the cornea and photophobia.

The Phase 1/2 clinical trial for AVR-RD-02 for Gaucher disease is actively recruiting in Australia and Canada, with additional sites planned in the United States. Patient enrollment has commenced, and we expect to dose the first patient in the second quarter of 2020.

Our AVR-RD-03 program for Pompe disease is currently in preclinical development with the first IND-enabling preclinical study initiated in 2019.

We continue to seek opportunities to expand our approach to other rare and non-rare diseases. We plan to identify and develop future product candidates through our own internal research efforts as well as through collaborations with leading researchers worldwide.

Plato is our gene therapy platform designed to provide the foundation for the potential worldwide commercialization of our gene therapies, if approved. It is an *ex vivo* gene therapy platform incorporating multiple upgrades including a four-plasmid lentiviral vector designed to optimize vector copy number, transduction efficiency and resulting enzyme activity; a closed, automated manufacturing system designed to improve consistency and predictability of the drug product; and a personalized approach to conditioning using busulfan with TDM, which is designed to optimize safety and engraftment. These three process changes, or upgrades, were cleared by applicable regulatory bodies in the United States, Canada and Australia for use in the Phase 2 clinical trial of AVR-RD-01 for Fabry disease and the Phase 1/2 clinical trial of AVR-RD-02 for Gaucher disease. We intend to utilize the plato platform with these process changes for all future patients enrolling in our Phase 2 clinical trial of AVR-RD-01 for Fabry disease and our Phase 1/2 clinical trial for Gaucher disease. We developed the plato platform to form the backbone of our commercial programs, with the intent of replacing our original academic platform with improved solutions for delivering our gene therapy candidates to patients in multiple disease indications. We believe improvements from our plato platform may lead to better patient outcomes with our gene therapy candidates.

Included in our process optimization efforts is the development of a detailed plan for the more cost efficient and scalable manufacturing of our product candidates. We are establishing global manufacturing capabilities to support all aspects of the development and, if approved, the eventual commercialization of our gene therapies, from lentiviral vector production to cell processing. We also utilize a cryopreservation process that we believe will allow for the global distribution and, if approved, commercialization of our gene therapies. Key to our strategy is to continuously improve our technology and production processes and to leverage these improvements across our gene therapies.

Our Expertise

We are led by biopharmaceutical experts with extensive experience in gene and cellular therapy, and rare diseases. Our team has broad expertise in the clinical, regulatory and commercialization aspects of rare diseases as well as process development and manufacturing for cellular therapies. Members of our management team have held senior positions at Shire, Genzyme, Novartis, GlaxoSmithKline, Lonza, Spark Therapeutics, Biogen, AveXis and other companies pursuing development, manufacturing and commercialization of gene, cellular and other therapies to treat rare diseases.

Our Strategy

Our goal is to develop and commercialize potentially curative lentiviral-based gene therapies for patients and expand the use of this approach to treat a number of diseases potentially addressable by our *ex vivo* gene therapy platform. Key elements of our strategy include:

- *Rapidly Advance Our Initial Gene Therapies Targeting Lysosomal Diseases.* We are initially targeting lysosomal diseases and are developing a deep pipeline of four gene therapies to treat Fabry disease, Gaucher disease, cystinosis and Pompe disease. We intend to continue rapidly advancing these gene therapies and obtain efficacy data in patients from these development programs. Five patients have been dosed in the investigator-sponsored Phase 1 clinical trial of AVR-RD-01 for Fabry disease, and enrollment is complete. Four patients have been dosed to date in our company-sponsored Phase 2 clinical trial of AVR-RD-01, and we are actively recruiting additional potential patients for our sites in Australia, Canada and the United States. AVR-RD-04 is currently being studied by our collaborators at UCSD in a Phase 1/2 investigator-sponsored clinical trial, and the first patient was dosed in October 2019. Enrollment has commenced for the Phase 1/2 clinical trial for AVR-RD-02 for Gaucher disease, and we are actively recruiting potential patients in Australia and Canada, with additional sites planned in the United States. In addition, we intend to pursue pathways for accelerated review and approval of our product candidates by the FDA and international regulatory authorities through programs such as the Regenerative Medicine Advanced Therapies, or RMAT, program in the United States.
- *Continue Implementing Our Plato Platform with Refined Approach to Conditioning, Enhanced Vector Technology and Optimized Manufacturing Processes.* We believe our innovations in viral vector design, cellular manufacturing, cryopreservation, and other related processes are important steps towards advancing the field of lentiviral-based gene therapy and realizing its full potential to treat a number of diseases. Our plato platform is designed to provide the foundation for the potential worldwide commercialization of our gene therapies, if approved, and incorporates a four-plasmid lentiviral vector designed to optimize vector copy number, transduction efficiency and resulting enzyme activity. We have developed a manufacturing process that we believe is both reproducible and scalable, and we believe our closed, automated manufacturing system will enable us to deliver our gene therapies to patients at an industrialized scale. In addition, we believe our personalized approach to conditioning using busulfan with TDM will enable us to pursue early intervention for the treatment of lysosomal diseases and expand into a wide range of diseases where lentiviral-based gene therapy has not been previously utilized. We will continue to leverage advancements in stem cell transplantation in order to improve patient safety and tolerability of our lentiviral-based gene therapies.
- *Build Global Infrastructure to Reach Patients Across the World.* Lysosomal diseases afflict patients globally and we intend to continue building global infrastructure in order to provide treatment to patients around the world. We are currently conducting clinical trials across multiple geographies, including the United States, Canada and Australia, with plans to potentially expand to other geographies including Japan, Europe and Israel. We have established a global network of suppliers and contract manufacturing organizations, or CMOs.
- *Leverage Our Approach Beyond Our Initial Indications.* We are initially developing gene therapies for the treatment of four different lysosomal diseases and believe that we will gain significant learnings and technical insights from these programs. We intend to leverage our technology and insights to treat a number of rare and non-rare diseases where we believe our lentiviral approach has transformative potential.

Our Approach

We develop therapies utilizing our *ex vivo* lentiviral-based gene therapy approach to transform a patient's own cells into a drug product. Our gene therapies employ lentiviral vectors that are designed to result in stable integration of the desired genes in the chromosomes of the stem cells such that they are permanently maintained in the cell and can be reproduced as the cell divides. We focus on delivering our lentiviral-based gene therapies to patient-derived hematopoietic stem cells, which are primitive stem cells that develop into all types of blood cells, including white blood cells, red blood cells and platelets. To accomplish this, we harvest a patient's hematopoietic stem cells and modify them *ex vivo* to add the equivalent of a functional copy of the gene that is defective in the target disease. We then infuse the modified cells back into the patient. Our gene therapies are designed to be administered to the patient as a one-time therapy following a TDM conditioning regimen.

We are initially focused on employing our approach to treat and potentially cure lysosomal diseases. These diseases have well-understood biologies, identified patient populations, established standards of care yet with significant unmet medical needs, and represent large markets with approximately $4.0 billion in worldwide net sales in 2019. We believe our *ex vivo* lentiviral-based gene therapy approach can be industrialized into a robust, scalable and, if approved, commercially viable process that will allow us to deliver our potentially curative therapies to patients across different geographies with these and other serious monogenic disorders.

Advantages of Our Lentiviral-Based Gene Therapy Approach

We believe lentiviral-based gene therapy provides numerous advantages, including:

- *Durable Benefit.* Lentiviral vectors have the potential to provide life-long benefits with a single dose. Lentiviral vectors can integrate stably into the genome of hematopoietic stem cells and, when these cells replicate, they pass the integrated genes on to their progeny cells.
- *Systemic Therapeutic Effect.* Progeny cells circulate systemically and may migrate into tissues and therefore have the ability to provide therapeutic benefit to affected tissues and organs throughout the body. In addition, we believe that the busulfan conditioning regimen used in our plato platform has the potential to allow our gene therapies to cross the blood-brain barrier, a feature which may yield therapeutic benefit in diseases that have a central nervous system component.
- *Function cell correction.* Lentiviral-based gene therapy has the potential to restore functional proteins in CD34+ stem cell daughter cells such as macrophages.
- *History of Safety in Precedent Third Party Clinical Trials.* No instances of insertional oncogenesis or leukemogenesis from lentiviral vectors have been observed in clinical trials in which over 350 total patients have been treated.
- *Broad Patient Applicability.* Lentiviral-based gene therapies have been used to deliver treatments to patients of all ages, including children, and to patients who may be ineligible for other types of gene therapy due to the presence of preexisting antibodies that detect viral vectors and trigger the immune system to destroy the vector and cells infected by the vector.
- *Larger and Varied Payloads.* In contrast to other viral vectors, lentiviruses have the capacity to carry larger gene sequences, which allow them to potentially address a large variety of indications.

Strategic Selection of Our Initial Indications

There are approximately 50 identified lysosomal diseases, which are characterized by an abnormal toxic build-up of substrates and their metabolites in the body's cells. We are initially targeting Fabry disease, Gaucher disease, cystinosis and Pompe disease. Each of these diseases affects a meaningful number of patients, has a suboptimal standard of care with unmet medical need and, we believe, is appropriate for lentiviral-based gene therapy. We believe our approach addresses the shortcomings of existing therapies where patients' disease continues to progress despite chronic dosing and that our approach has the potential to halt progression of these diseases.

Clinical proof of concept already exists for allogeneic bone marrow transplant in some lysosomal diseases, supporting the notion that transplantation of cells that produce normal enzyme can have clinical impact on disease. Experience with allogeneic bone marrow transplant in patients with Gaucher disease provides evidence to support our *ex vivo* gene therapy approach. Additionally, in cystinosis, transplant of human bone marrow and hematopoietic stem cells into a mouse model demonstrates proof of concept efficacy for transplant. Our *ex vivo* gene therapy approach allows patients to be their own cell donor, eliminating the need to find a matched bone marrow donor, while reducing the risk of complications related to the immunosuppression regimens required in allogeneic cell transplant in order to prevent both rejection and graft versus host disease.

Expanding the Utility of Lentiviral-Based Gene Therapy with TDM-Enabled Conditioning Regimen

A core part of our approach is to expand the use of lentiviral-based gene therapy to treat numerous diseases. We believe that we will be able to demonstrate durable effects in our targeted diseases utilizing a single myeloablative agent, busulfan, which we have transitioned to as part of implementing our plato platform. Busulfan is mildly immunosuppressive and is designed to be personalized to each patient using TDM to achieve the desired level of conditioning to allow for gene therapy administration while limiting complications. We believe our approach to conditioning has the potential for reduced short- and long-term toxicities and effective long-term engraftment. If realized, we believe these benefits may promote lentiviral-based gene therapy as a therapeutic option for less acutely severe diseases or diseases with approved therapies in which large unmet medical needs remain.

Prior to the reintroduction of *ex vivo* modified stem cells, a conditioning regimen is generally required to remove existing stem cells from the bone marrow in order to create space for the modified stem cells. Creating sufficient space in the bone marrow for the lentivirally-modified hematopoietic stem cells is required to enable the cells to engraft long-term and produce their progeny cells. Ablation requires the use of cytotoxic drugs that can transiently compromise the patient's immune system, known as neutropenia, and ability to form blood clots, known as thrombocytopenia.

Since its first clinical use in 2003, lentiviral-based gene therapy has been observed to be well-tolerated in third parties' clinical trials for rare diseases such as transfusion-dependent beta thalassemia, CALD, MLD, and ADA-SCID. Initially, the use of *ex vivo* lentiviral-based gene therapies was restricted primarily to the most severe diseases where the risks of the typical requirement for ablating the patients' bone marrow had a clinically justifiable risk/benefit profile. To date, over 350 patients have been treated with lentiviral-based gene therapies in third parties' and our rare disease clinical trials, and we believe the technology can be developed for other serious conditions based on a rigorous risk/benefit assessment. The ablation procedure, also known as the conditioning regimen, is typically an essential step in the *ex vivo* gene therapy treatment procedure and is administered prior to the gene therapy. The higher the level of conditioning, the greater the potential risk of more serious complications, such as veno-occlusive disease. However, we believe the risk of the more serious complications can be managed through utilization of TDM to enable careful titrating of exposure to the drug to a specific AuC. The conditioning regimen utilized as part of our plato platform includes TDM to assess how rapidly the individual patient metabolizes the conditioning agent so physicians can adjust the dose as needed, with a goal of minimizing side effects while maximizing the potential of durable engraftment. Such an approach could potentially allow the conditioning regimen to be performed during a limited hospital stay or potentially through an outpatient procedure, on a case-by-case basis as may be directed by the patient's physician. We believe our approach, utilizing a single myeloablative conditioning agent, busulfan, coupled with TDM designed to titrate to a specific AuC, has the potential to extend the reach of our gene therapies to a broad range of diseases as first-line therapies. Our goal is to broaden the applicability of lentiviral-based gene therapy by initially targeting monogenic diseases with an identified gene, recognized biology and that could potentially benefit from the sustained systemic delivery of an active protein.

plato: Our Commercial-Scale Platform

Since forming our company, we have centered our efforts on developing first-line gene therapies, based on preceding academic approaches. While we believe these approaches have been adequate for our development programs to date, key to our strategy is to continuously improve our technology and production processes and to leverage these improvements across our gene therapies, if approved. Plato is designed to provide the foundation for the potential worldwide commercialization of our gene therapies. It is an *ex vivo* gene therapy platform incorporating multiple upgrades including a four-plasmid lentiviral vector designed to optimize vector copy number, transduction efficiency and resulting enzyme activity; a closed, automated manufacturing system designed to improve consistency and predictability of the drug product; and a personalized approach to conditioning using busulfan with TDM, which is designed to optimize safety and engraftment. These three process changes, or upgrades, were cleared by applicable regulatory bodies in the United States, Canada and Australia for use in the Phase 2 clinical trial of AVR-RD-01 for Fabry disease and the Phase 1/2 clinical trial of AVR-RD-02 for Gaucher disease. We intend to utilize the plato platform with these process changes for all future patients enrolling in our Phase 2 clinical trial of AVR-RD-01 for Fabry disease and our Phase 1/2 clinical trial of AVR-RD-02 for Gaucher disease. We believe our plato platform may lead to better patient outcomes and will represent a significant advance in our industry towards achieving the quality and scale required for global commercialization of gene therapies.

Our plato platform is designed to feature:

- ***Large scale vector production***: We currently have manufacturing capabilities, through CMOs, at 200-liter bioreactor scale, with vector production capable of treating a substantial number of patients per year.
- ***Global reach***: Our automated, closed system for manufacturing is designed to allow for the flexible production of our gene therapies. The automated, closed manufacturing system is portable with proprietary AVROBIO algorithms which allow for efficient establishment of manufacturing capabilities in multiple geographies that can be expanded or adjusted as our global supply requirements evolve. We believe this approach will facilitate global manufacturing and shipping of our gene therapies, and will promote access to our products by patients and caregivers.
- ***Quality of manufacturing***: Our platform is designed to utilize current good manufacturing practices, or cGMP, and we believe our automated, closed manufacturing system may result in less production variability and reduce the risk of operator error, while enhancing the potency of the drug product. We believe these features will improve the quality of our gene therapies that are produced.
- ***Patient convenience***: Our gene therapies are cryopreserved, which is a feature designed to promote a longer shelf-life. We believe that a longer shelf-life will allow patients and clinics to schedule treatment sessions with greater convenience.
- ***Cost containment***: Our platform is designed to control fixed and variable expenses associated with manufacturing our gene therapies.

We believe the plato platform will form the backbone of our future commercialization efforts and our goal to take gene therapy mainstream.

Next Generation Vector Technology

We utilize our core expertise in the development and optimization of lentiviral vectors to continuously improve the vectors used in our gene therapies. We have made and expect to continue to make enhancements to our lentiviral vectors to improve safety, efficacy and efficiency. For example, clinical trials of AVR-RD-01 have primarily utilized our original academic three-plasmid-produced lentiviral vector, which we refer to as LV1. In December 2019 we dosed the fourth patient in our ongoing Phase 2 clinical trial of AVR-RD-01 using our proprietary four-plasmid lentiviral vector, which we refer to as LV2, and expect to dose all future patients in this trial with LV2. Our goal is to employ vectors that are state-of-the-art and that can be produced in a cost-effective and scalable manner.

Automated, Closed Manufacturing System

Our team has significant experience in cell processing and commercial-scale cellular therapy manufacturing. We have developed and are implementing a detailed plan for more cost efficient and scalable manufacturing of our gene therapies. In contrast to a number of other gene therapy companies that have not developed their commercial scale plans from the outset, we have executed on our plans to move to a closed suspension bioreactor system for vector production, as well as a closed, automated system for manufacturing our gene therapy product. Our move to a closed, automated manufacturing system was completed in 2019 as part of implementing upgrades from our plato platform, and in December 2019 the fourth patient in our ongoing Phase 2 clinical trial of AVR-RD-01 was dosed using the closed, automated manufacturing system. We believe our plato platform features the first automated, closed manufacturing system in CD34+ gene therapy.

Our manufacturing approach is intended to allow for the production of drug product using relatively small, self-contained devices, which may reduce our reliance on large traditional clean rooms that are expensive to establish and maintain. We believe our manufacturing approach may result in greater flexibility in the location of manufacture and help to control costs associated with traditional manufacturing. In addition, we believe our automated manufacturing process may reduce operator error and yield greater consistency and less variability in the manufactured drug product.

We currently have a CMO partner for the production of our cellular drug product in Australia and we have established two CMO partners in the United States who are currently preparing for production with cGMP-readiness for AVR-RD-01 and AVR-RD-02. We also are in the process of establishing a CMO partnership in Europe.

Optimization of Conditioning Regimen

The conditioning regimen that we have historically employed utilizes melphalan, a common chemotherapy drug, to ablate the patient’s bone marrow. As part of the upgrades to our plato platform, we have transitioned to utilizing busulfan, another chemotherapy drug, that has been in use since the 1950’s. Busulfan is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic stem cell transplantation for chronic myeloid leukemia. Busulfan is routinely used in conditioning regimens before allogeneic stem cell transplantations for both malignant and non-malignant conditions. It has also been used as a single-agent, or in combination with an immunosuppressive agent, such as cyclophosphamide, in conditioning regimens prior to *ex vivo* gene therapy transplants.

We believe that the transition to busulfan for our conditioning regimen may confer several advantages. For example, busulfan will permit utilization of TDM in our conditioning regimen, thereby enabling physicians to personalize the dosing to each patient by titrating over four days to enhance patient tolerability to the conditioning procedure and promote cell engraftment. By contrast, melphalan is administered once with no TDM, and may cause concern of conditioning-related toxicity across patients due to individual differences in metabolism of the drug. In addition, we believe that the utilization of busulfan in our single-agent myeloablative conditioning regimen may have the potential to allow our gene therapies to cross the blood-brain barrier, a feature which may yield therapeutic benefit in diseases that have a central nervous system component, such as Fabry disease, Gaucher disease, Pompe disease and other rare and non-rare diseases. Finally, our busulfan conditioning regimen is designed to create more space in the ablated bone marrow compared to melphalan and may increase the average VCN of the patient bone marrow following treatment with the drug product, which are features that we believe will promote better cell engraftment and durability of the gene therapy.

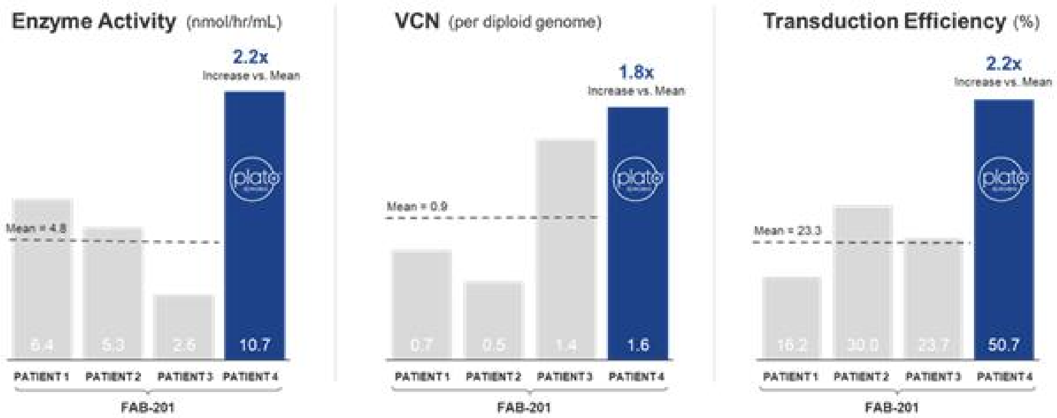
We are aware that there have been cases of therapy-related myelodysplastic syndrome, or t-MDS, a type of blood disorder that is a potential precursor to acute myeloid leukemia, in patients with pre-existing cancer where busulfan treatment was posited to be a contributing factor to this secondary malignancy. However, we have reviewed over 700 published cases of busulfan exposure preceding bone marrow transplant, hematopoietic cell transplant, or *ex-vivo* gene therapy for non-malignant indications, of which 648 were from peer-reviewed literature. Of the 648 busulfan exposures reported in peer-reviewed literature, none of the cases reported t-MDS. Of the 67 exposures reported in non-peer-reviewed published abstracts, 66 reported no cases of t-MDS resulting from busulfan exposure, and in one case it was reported that a patient developed t-MDS. In that case, which has not yet been peer-reviewed, busulfan treatment was posited to be a contributing factor. We believe that due to the presence of other confounding factors in the patient, the cause of that patient's t-MDS has not been conclusively determined. In the future we may also utilize molecular cytogenetic screening to further reduce such risks to patients.

While the busulfan conditioning regimen is more intensive than the original conditioning regimen that utilizes melphalan, we believe it is still milder than some of the more aggressive conditioning regimens associated with gene therapies for other diseases, such as when busulfan is used in combination with cyclophosphamide, used at a higher dose, or when TDM is not applied. Furthermore, we believe our conditioning regimen may produce the desired effect while potentially allowing for a limited hospital stay or potentially for an outpatient procedure, on a case-by-case basis as may be directed by the patient's physician.

The fourth patient in our Phase 2 trial of AVR-RD-01 for Fabry disease received a precision dosing conditioning regimen with busulfan as part of the plato platform, while the first patient in the Phase 1/2 trial of AVR-RD-04 for cystinosis received busulfan but not as part of the plato platform. In February 2020 we announced that these two patients both had rapid neutrophil and platelet count recovery, with a trajectory that was similar to the patients who enrolled earlier in the trials of AVR-RD-01 and who received a melphalan conditioning regimen. Side effects, which included nausea, mucositis, fever, rash and hair loss, developed eight to 10 days after dosing with busulfan and then resolved quickly.

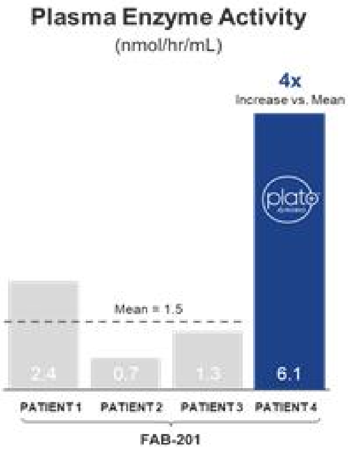
Initial plato Data

In December 2019, we announced that the first patient had been dosed using our plato platform, who is the fourth patient dosed in our ongoing Phase 2 clinical trial of AVR-RD-01. The figures below, which we presented in February 2020, summarize the enzyme activity, VCN and transduction efficiency measurements of the drug product produced with our plato platform for the fourth patient in the Phase 2 trial of AVR-RD-01 for Fabry disease, as compared to the same individual values and mean of such values observed in the drug product for the first three patients in the same trial, each of whom were dosed prior to our implementation of the plato platform. We refer to the Phase 2 trial of AVR-RD-01 as FAB-201.



***Note**: 0.1 VCN is indicative of approx. 5-10% of all nucleated circulating blood cells having an average of 1-2 copies of the transgene*

The figure below summarizes the *in vivo* plasma enzyme activity for all four patients in our Phase 2 clinical trial of AVR-RD-01, measured as of one-month post-treatment.

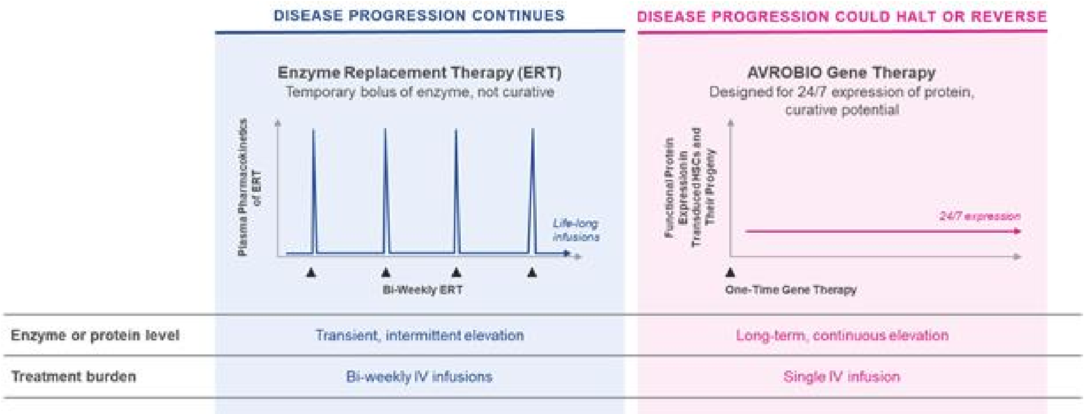


The investigational drug product used to dose the first patient in the AVR-RD-04 program for cystinosis, which was produced at the University of California, Los Angeles and included a four-plasmid vector but not our proprietary LV2 vector or plato's automated manufacturing process, exhibited a drug product VCN of 2.1 and a transduction efficiency of 76.0%. The investigational drug product and VCN assay are different for each trial.

Advantages of Our Approach over Existing Therapies

We believe our gene therapy solutions offer several potential advantages over existing therapies for lysosomal diseases, including:

- *Curative Impact That Has The Potential to Halt or Reverse Disease Progression.* Existing ERTs for Fabry, Gaucher and Pompe and oral therapies for cystinosis provide some therapeutic benefit to patients. However, because of their suboptimal pharmacokinetics, these ERTs only transiently increase plasma enzyme levels and the therapies for cystinosis require multiple doses throughout the day. In contrast, our lentiviral-based gene therapies are designed to enable the body to constantly produce the functional enzyme or other protein. This can potentially halt pathological damage and, depending on the targeted indication and organ system, may even reverse disease progression. Our lentiviral-based gene therapies may provide potentially curative treatment to patients. This concept is illustrated in the graphs below.



- *Durable, Single-Dose Treatment.* Our gene therapies offer the potential for a single dose to replace life-long, bi-weekly infusions or daily oral therapies that are often accompanied by numerous side effects and impact patients' quality of life. Our gene therapies are designed to transform the patient's own cells into a drug product that enables the continuous delivery of functional enzyme or other protein throughout the body after a single dose.
- *Reduced Treatment Cost Over a Patient's Lifetime.* Existing ERTs and oral therapies can cost millions of dollars over a patient's lifetime because these therapies require frequent doses of expensive treatments to manage symptoms. Our single-dose gene therapies are designed to replace the costly chronic intravenous and oral therapies that are the current standard of care for patients with lysosomal diseases.

AVR-RD-01, Our Gene Therapy for Fabry Disease

We are developing AVR-RD-01 for the treatment of Fabry disease. We manufacture AVR-RD-01 from stem cells that are first harvested from the patient, modified to add the gene that encodes for AGA, and then infused into the patient. AVR-RD-01 is currently being evaluated in an investigator-sponsored Phase 1 clinical trial and a company-sponsored Phase 2 clinical trial. A total of nine patients have been dosed across both trials as of March 6, 2020.

Disease Overview

Fabry disease is a rare lysosomal disease associated with significant morbidity and early mortality. It is caused by a gene defect that causes a deficiency of AGA, which breaks down a particular type of fat in the body's cells known as globotriaosylceramide, or Gb3. As Gb3 and other related substrates increase in patients with Fabry disease, these become toxic to the patient's cells. Gb3 and other glycosphingolipids accumulate and result in damage to the kidneys, heart and brain. Accumulation of Gb3 in tissues such as the heart and the vascular system can lead to life threatening vascular blockages and thus stroke and heart attacks. In addition, high levels of Gb3 substrate accumulation in the kidney can cause kidney failure. Gb3 can also accumulate in other tissues, such as the nervous system where it leads to debilitating pain. Due to end-stage renal disease and other life-threatening complications associated with Fabry disease, the average life expectancy in affected males is approximately 58 years of age.

Most patients with Fabry disease begin experiencing chronic pain in childhood but are often not diagnosed with Fabry disease until their twenties, due to a broad variation in patient symptoms. Over 1,000 gene mutations associated with Fabry disease have been identified. It is estimated that Fabry disease is diagnosed in approximately one in 40,000 males and one in 118,000 females in the United States, but studies have suggested that a larger number of patients may be undiagnosed.

Fabry disease is an X-linked disorder, meaning the gene that is responsible is located on the X chromosome. Because males have only one X chromosome, an abnormal copy of the gene that causes Fabry disease is sufficient to cause the disease. However, unlike other X-linked disorders, where female carriers of an abnormal gene are usually unaffected, Fabry disease also often causes significant morbidity in females who inherit one abnormal copy and one normal copy of the gene associated with the disease.

Limitations of Current Therapies

Fabry disease is primarily treated with periodic infusions of ERT consisting of AGA enzyme over the patient's lifetime. The most commonly prescribed ERTs for Fabry disease are Fabrazyme, marketed by Sanofi Genzyme, and Replagal, marketed by Shire, which was acquired by Takeda Pharmaceutical Company Ltd. In 2019, Fabrazyme and Replagal generated worldwide net sales of approximately €813 million euros and ¥50 billion Japanese yen, respectively. The annual average cost to the healthcare system per patient prescribed Fabrazyme in the United States is approximately $320,000. In addition, because ERTs are not curative and only slow, but do not halt, the progression of disease, patients deteriorate and the healthcare system incurs significant costs associated with recurring medical interventions.

Although ERT provides therapeutic benefit and can reduce Gb3 substrate levels and extend a patient's life expectancy, ERT requires chronic infusions throughout the patient's life. Patients prescribed ERT generally receive an infusion every other week. However, because of their suboptimal pharmacokinetics, ERTs only temporarily increase plasma enzyme levels. As a result, patients with Fabry disease prescribed ERT continue to have disease progression, including ongoing decline in renal function, potentially including renal failure, cardiovascular disease and ongoing debilitating pain including periods of severe pain crisis. Physicians report that patients have recurrence of symptoms as the therapeutic effect of ERT wanes between bi-weekly treatments.

Alternatives to ERT for patients with Fabry disease are limited. Galafold (migalastat), an oral therapy marketed by Amicus, was approved by the European Medicines Agency, or EMA, in May 2016, and by the FDA in August 2018. Amicus reports that only 35% to 50% of the gene mutations associated with Fabry disease are amenable to migalastat.

Our Solution

We are developing AVR-RD-01 to halt or reverse disease progression and potentially cure patients with Fabry disease with a single dose of the patient's own hematopoietic stem cells modified in an *ex vivo* procedure. AVR-RD-01 is a lentiviral-based gene therapy that contains a codon-optimized human gene and is designed to maximize the likelihood of sustained AGA production by hematopoietic stem cells and their progeny.

We believe that AVR-RD-01 offers a promising treatment for Fabry disease for the following reasons:

- *One-Time Delivery.* Lentiviral-based gene therapy provides the potential to transform a patient's own cells into a drug product that enables the continuous delivery of active enzyme throughout the body after a single dose.
- *Proven Biology.* Years of observations of patients prescribed ERT indicate that even partial plasma AGA activity is associated with improved outcomes. Increased AGA enzyme activity is able to reduce Gb3 levels in multiple cells and tissues supporting the ability of AGA in the plasma to enter lysosomes and degrade Gb3 in a process referred to as cross correction.
- *Wide Therapeutic Window.* We believe that even partial enzyme activity, if continuous, has the potential to provide long-term therapeutic benefit. A wide range of levels of plasma AGA activity has been demonstrated to be both safe and effective in preclinical studies, reducing the need for precise regulation of enzyme expression levels and reinforcing that overexpression of AGA is not associated with increased safety risks.
- *Mutation Independent.* AVR-RD-01 is designed to increase plasma and leukocyte AGA levels in a patient's cells, regardless of which of the more than 1,000 specific mutations underlie the patient's disease.

Ongoing Multicenter Investigator-Sponsored Clinical Trial

In an ongoing Phase 1 clinical trial of AVR-RD-01 being conducted by the University Health Network, or UHN, and sponsored by Fabry Disease Clinical Research and Therapeutics, or FACTs, at three centers in Canada, a total of five patients with Fabry disease who have been treated with ERT for at least six months have been enrolled, and enrollment is complete. The protocol for this clinical trial originally provided that ERT for these patients would be suspended one month prior to receiving AVR-RD-01 and then resumed one month after the AVR-RD-01 treatment and continued at bi-weekly intervals. The trial protocol was subsequently amended to allow the investigator team, at their discretion, to discontinue ERT six months after treatment with AVR-RD-01. Three of the five patients in the clinical trial have discontinued the regular bi-weekly treatments with ERT and all three remain off ERT as of March 6, 2020.

The primary goal for this clinical trial is to assess the safety and toxicity of AVR-RD-01 as measured by the frequency or severity of clinically notable abnormal vital signs and laboratory values and the frequency or severity of treatment-related adverse events. The safety of our initial, academic-based conditioning regimen is also being assessed in this clinical trial.

A secondary objective for this clinical trial is to obtain preliminary efficacy signals of AVR-RD-01 therapy as assessed by AGA enzyme activity. Plasma and leukocyte AGA enzyme activity derived from administration of ERT decreases rapidly after administration with no residual plasma or leukocyte activity remaining approximately one day after treatment. To evaluate the ability of AVR-RD-01 to increase enzyme activity, the level of AGA activity was assessed in a patient immediately prior to the administration of the patient's next dose of ERT, when limited or no plasma or leukocyte AGA activity from previously-administered ERT dose would be expected.

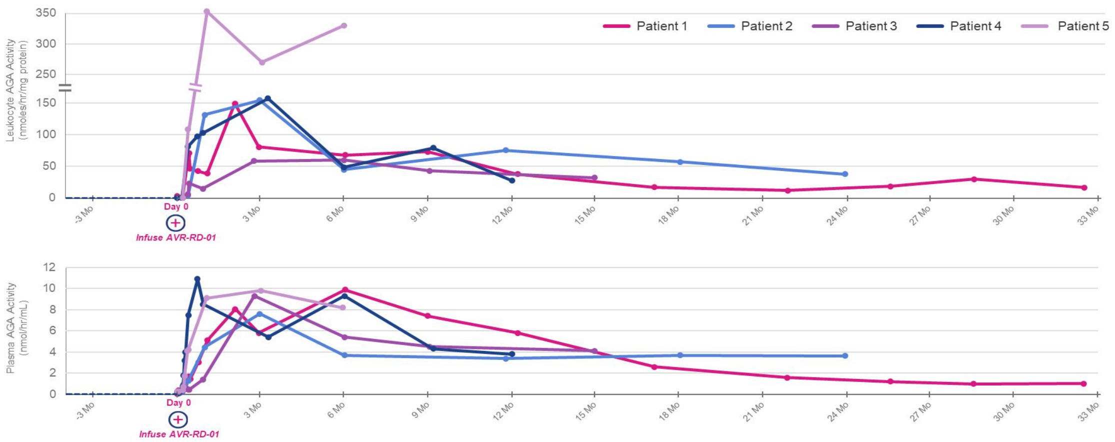
All five patients in this clinical trial have been dosed. To date, the treatment was generally well-tolerated with no serious adverse events, or SAEs, related to the study drug. In addition, in all five patients, all of whom are males with classic Fabry disease, the level of plasma and leukocyte AGA enzyme activity began to rise after infusion. In each of the patients for whom data is available up to 12 months or later, plasma and leukocyte AGA enzyme activity was observed to increase from nearly undetectable levels before treatment to a peak within six months after treatment, followed by a decline and trending to stabilize to levels above the range for males with classical Fabry disease, defined as less than 1 nmol/hr/ml. We believe that the steep initial increase reflects AGA enzyme activity from the early progeny of the transduced stem cells, while the subsequent decline and stabilization in AGA enzyme levels reflect a shift from short term progenitor cells towards the gradual secretion of AGA enzyme by long-term engraftment cells that become more predominant over time.

AGA Enzyme Activity

As of 32 months after receiving AVR-RD-01, the first patient's plasma and leukocyte AGA enzyme activity levels continued to be above the range for males with classical Fabry disease. Based on the level of endogenously produced enzyme activity, at the 18-month follow-up visit for this patient, the investigator team for the trial made a clinical decision to discontinue the bi-weekly ERT and the patient remains off ERT as of 32 months post-treatment with AVR-RD-01. Additionally, the third and fourth patients in this clinical trial discontinued ERT one month prior to receiving AVR-RD-01 and voluntarily elected not to resume ERT. These patients remain off ERT as of 15 and 12 months post-treatment with AVR-RD-01, respectively. The second and fifth patients have elected to continue receiving concurrent ERT. Plasma and leukocyte AGA enzyme activity levels in all five patients remained above the range for males with classical Fabry disease, defined as less than 1 nmol/hr/ml, as of 32 months, 24 months, 15 months, 12 months and six months after treatment, respectively. We believe these results, particularly from the patients in the trial with longer-term AGA data points reported, support the potential of AVR-RD-01 to drive functional enzyme production for long durations.

The following graphs present the plasma and leukocyte AGA activity data following AVR-RD-01 treatment in all five patients over various points in time.

Phase 1: Leukocyte and Plasma AGA activity* post-AVR-RD-01 treatment



*   For patients on ERT, enzyme activity is measured at trough, where applicable.
Note: Dotted line illustrative only.

Lyso-Gb3 Levels

The substrate, Gb3, and its toxic metabolite, known as lyso-Gb3, are considered surrogate markers for disease activity and treatment response for Fabry disease. In the case of ERT-naïve patients and patients who have discontinued ERT, we believe that reductions in Gb3 levels following treatment with gene therapy are likely driven by the therapeutic effect of gene therapy. In four of the five patients in the Phase 1 clinical trial of AVR-RD-01, we have observed plasma lyso-Gb3 at levels post-treatment that are lower than the levels observed when the patient received only ERT prior to administration of AVR-RD-01, which we refer to as baseline ERT levels. We define baseline ERT for these Phase 1 patients as the mean of the plasma lyso-Gb3 values reported prior to initiating mobilization. Based on the latest available efficacy data, these four Phase 1 patients exhibited reductions in plasma lyso-Gb3 levels ranging between 26% and 47% compared to their baseline ERT levels. With respect to the fourth patient, who discontinued ERT six months following administration of AVR-RD-01, we observed an initial decline in plasma lyso-Gb3 levels through six months post-treatment compared to baseline ERT, and a 23% increase in plasma lyso-Gb3 levels at twelve months post-treatment compared to baseline ERT. This patient's plasma lyso-Gb3 levels remain within the range for the Fabry disease patients on ERT observed in this Phase 1 clinical trial.

The following graphs present the plasma lyso-Gb3 data following AVR-RD-01 treatment in all five patients over various points in time, as well as each patient's ERT status and the change in plasma lyso-Gb3 levels from baseline.

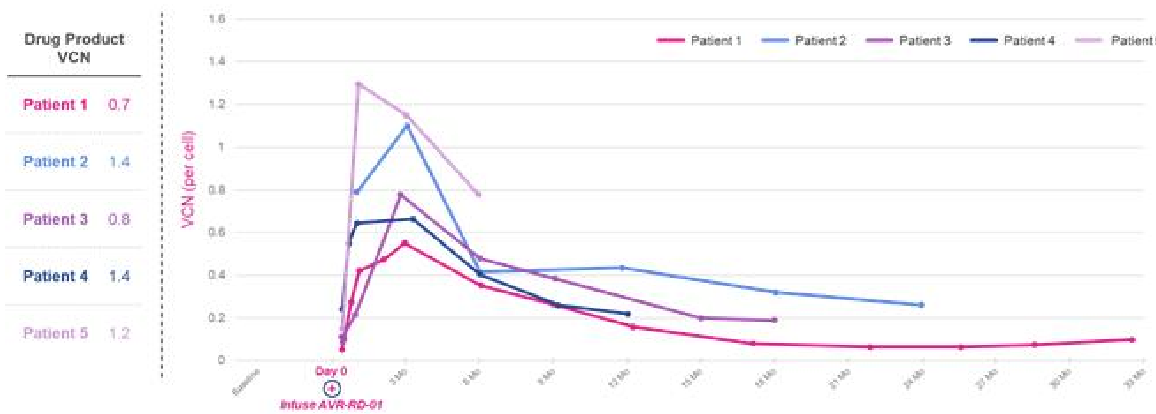
Phase 1: Plasma lyso-Gb3 levels and ERT status post-AVR-RD-01 treatment

Vector Copy Number

VCN, which is expressed as VCN per diploid genome, refers to the average number of copies of the lentiviral-vector inserted gene that are integrated into the genome of a cell, and is another measure that can be used to help assess the durability of a gene therapy. We believe that different diseases may require varying levels of VCN based on the underlying condition, and therefore VCN measurements across different diseases should be assessed separately. For example, a VCN of 0.1 may represent 5% to 10% of all nucleated circulating blood cells carrying one to two copies of the inserted gene, which we believe may be sufficient to result in clinically meaningful AGA enzyme activity in the case of Fabry disease, as suggested by our preliminary interim data from our ongoing clinical trials of AVR-RD-01.

The following graph presents the VCN data following AVR-RD-01 treatment in all five patients over various points in time, as well as the VCN of the drug product produced for each patient.

Phase 1: Average VCN* in Nucleated Blood Cells post-AVR-RD-01 treatment



* Average VCN refers to the average number of copies of the lentiviral-vector inserted gene that are integrated into the genome of a cell, for a given cell population.

Safety

Preliminary safety data indicate AVR-RD-01 was generally well-tolerated with no SAEs related to the study drug. Adverse events, or AEs, were consistent with expectations for the melphalan conditioning regimen prescribed by the study protocol. As of the most recent safety cut-off date of November 26, 2019, there were 130 AEs reported, 115 of which were assessed by the investigator as being possibly, probably or definitely related to protocol treatment or procedures (which includes apheresis, stem cell transplant procedure, blood draws, insertion of central catheters, drugs used for mobilization of stem cells and/or conditioning, and the drug product). Two SAEs were reported through the safety data cut-off date of November 26, 2019, which included one report of Grade 3 febrile neutropenia and one report of Grade 2 thrombophlebitis, each occurring following the conditioning regimen and treatment with AVR-RD-01. Both SAEs have subsequently resolved. One event, the development of a left thigh mass, was originally reported as an SAE but has now been considered by the study investigator as not serious and has resolved in the patient. No new AEs have been reported for the first patient since January 17, 2018, the second patient since May 9, 2018, the third patient since August 6, 2018, the fourth patient since August 6, 2018 or the fifth patient since August 2019. In addition, investigators observed a temporary suppression of absolute neutrophil counts and platelets, which is an expected consequence of the conditioning regimen. These decreases were transient and not associated with any negative long-term impact on the patients. Neutrophil and platelet counts recovered after dosing. Because this clinical trial is ongoing, safety data are preliminary and subject to change. Subsequent to November 26, 2019, we have not been notified by the investigators in this clinical trial of any suspected SAEs related to the study drug.

Pre-existing low anti-AGA antibody titers have been detected in four patients in the Phase 1 trial. We believe none of these are of clinical relevance.

Phase 2 Multinational Clinical Trial

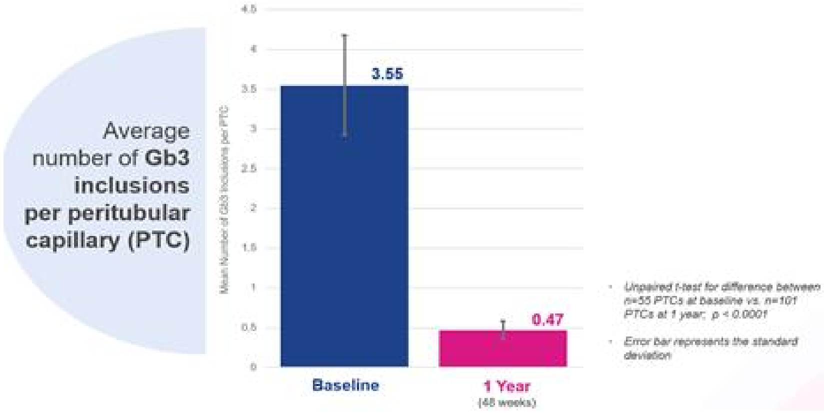
We are sponsoring an open label, multinational Phase 2 clinical trial of AVR-RD-01. This study was initiated in June 2018 in Australia and enrollment in this Phase 2 clinical trial is ongoing. Eight to 12 treatment-naïve males, 16 to 50 years old, with Fabry disease are expected to be enrolled in this trial. Our objectives for this trial are to assess safety and efficacy as measured by multiple indicators, such as AGA enzyme activity, Gb3 and lyso-Gb3 levels in blood and various tissues, kidney and cardiac function, gastrointestinal symptoms, and pain and quality of life scores. All enrolled patients will receive a single treatment with AVR-RD-01 and will be followed for 48 weeks to measure safety and efficacy. We have opened two U.S. sites for our ongoing Phase 2 clinical trial and are actively recruiting potential patients for our sites in Australia, Canada and the United States. We are also engaged in discussions with the Pharmaceuticals and Medical Devices Agency, or PMDA, regarding potential future clinical development of AVR-RD-01 in Japan.

As of March 6, 2020, four patients have been dosed in the Phase 2 clinical trial. For the fourth patient, we transitioned the lentiviral vector from LV1 to our optimized proprietary LV2 from our plato platform. All future patients in this clinical trial will be dosed using the plato platform, which we believe will further improve the efficacy and further enhance the safety of our lentiviral-based gene therapy. Because the transition to LV2 only impacts the *ex vivo* cell transduction process, and not the actual AGA enzyme that is produced by the transduced cells, or drug product, we believe this transition will be supported with *in vitro* comparability studies.

Kidney Biopsy

The primary efficacy endpoint of our Phase 2 clinical trial is the change from baseline in the average number of Gb3 inclusions per peritubular capillary, or PTC, as measured in a patient kidney biopsy one year (48 weeks) after treatment with AVR-RD-01. Gb3, also referred to as GL-3, is a type of fatty substrate that builds in the cells of Fabry patients, resulting in damage to organs such as kidneys and heart. PTCs, also referred to as kidney interstitial capillaries, or KICs, in Fabry clinical trials, convey blood after filtration in the glomeruli, enabling the blood to eventually exit the kidney and return to the circulatory system. In July 2019, we announced that the first patient in our Phase 2 clinical trial, who had not previously received ERT, exhibited a reduction from an average of 3.55 Gb3 inclusions per PTC at baseline to an average of 0.47 inclusions per PTC one year after administration of AVR-RD-01, representing an 87% reduction and a numerical decrease of 3.08. The following figure illustrates this decrease in average Gb3 inclusions per PTC for this patient.

Phase 2: Patient 1 exhibited 87% substrate reduction in kidney biopsy



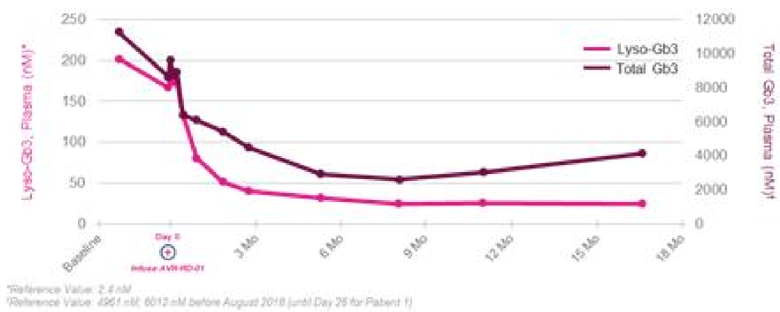
***Baseline**: The last available, non-missing observation prior to AVR-RD-01 infusion*
***Note:** With respect to Fabry disease clinical trials, Gb3 inclusions per PTC is interchangeable with GL-3 inclusions per KIC*

Lyso-Gb3 Levels

The first patient in our Phase 2 trial had an 87% reduction in plasma lyso-Gb3 levels as of eighteen months post-treatment with AVR-RD-01, and the third patient had a plasma lyso-Gb3 reduction of 52% as of six months post-treatment with AVR-RD-01. Plasma lyso-Gb3 data are also available for the second patient in the Phase 2 trial, up to twelve months post-treatment with AVR-RD-01. This patient has an N215S genotype, which is associated with a late-onset cardiac variant phenotype and does not typically result in Gb3 accumulation in the kidney or skin. Accordingly, this patient's skin and kidney biopsy had low levels of plasma Gb3 and lyso-Gb3 at all measurements, including at baseline. Although we expect that data obtained from this patient will not provide meaningful insight on the efficacy endpoints in our Phase 2 clinical trial, including kidney and skin biopsies, there may be other important insights derived from data collected from this patient in the Phase 2 clinical trial.

The following table presents the plasma lyso-Gb3 data following AVR-RD-01 treatment in the first and third patients of the Phase 2 trial.

Phase 2: Patient 1 Plasma lyso-Gb3 reductions post-AVR-RD-01 treatment



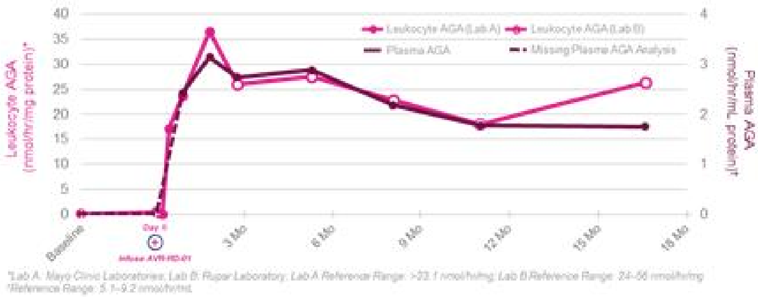
Phase 2: Patient 3 Plasma lyso-Gb3 reductions post-AVR-RD-01 treatment

AGA Enzyme Activity

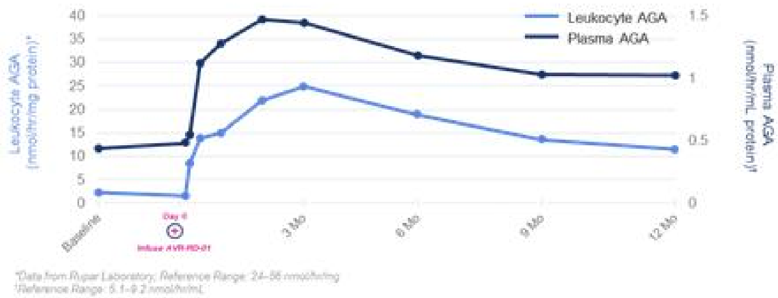
In the first two patients in our Phase 2 clinical trial, for whom data is available out to 18 and 12 months, respectively, plasma and leukocyte AGA enzyme activity was observed to increase from nearly undetectable levels before treatment to a peak within three months after treatment, followed by a decline and trending to stabilize to levels above the range for males with Fabry disease, defined as less than 1 nmol/hr/ml. The third patient in the Phase 2 trial exhibited a rapid increase in plasma and leukocyte AGA enzyme activity from nearly undetectable levels before treatment to a peak within the first seven days after treatment in the case of plasma enzyme activity and within the first 14 days after treatment in the case of leukocyte enzyme activity, followed by a decline and subsequent increase observed at month six. Similar to the results observed in the investigator-led Phase 1 trial of AVR-RD-01, we believe that the steep initial increase reflects AGA enzyme activity from the early progeny of the transduced stem cells, while the subsequent decline and stabilization in AGA enzyme levels reflect a shift from short term progenitor cells towards the gradual secretion of AGA enzyme by long-term engraftment cells that become more predominant over time.

The following graphs present the plasma and leukocyte AGA activity data following AVR-RD-01 treatment in the first, second and third patients of the Phase 2 trial.

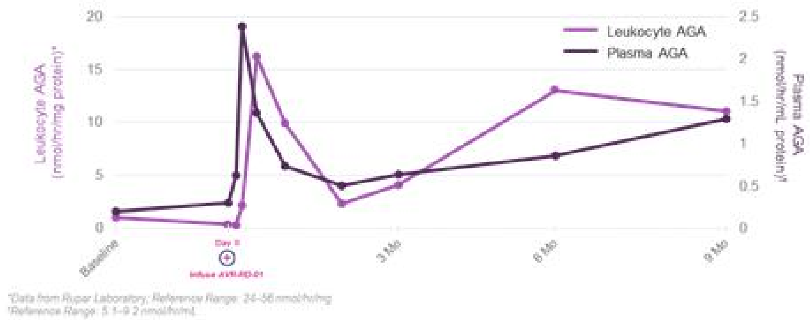
Phase 2: Patient 1 Leukocyte and Plasma AGA activity post-AVR-RD-01 treatment



Phase 2: Patient 2 Leukocyte and Plasma AGA activity post-AVR-RD-01 treatment



Phase 2: Patient 3 Leukocyte and Plasma AGA activity post-AVR-RD-01 treatment



Skin Biopsy

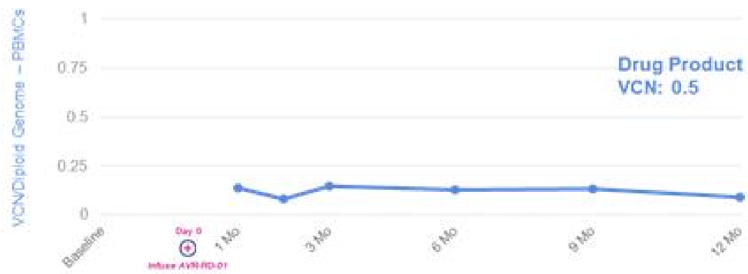
Skin biopsies have been performed on the first three patients in the Phase 2 trial and evaluated by two independent blinded readers using a standard scoring system for Gb3 accumulation and clearance. The scoring system has a range of zero to 3, with a score of zero representing none or trace accumulation, and a score of 3 representing severe accumulation. At six and 12 months post-treatment with AVR-RD-01, skin biopsy assessment revealed that the first patient achieved a substantial reduction in substrate inclusions in capillary endothelium of the skin. This patient scored a 3 at baseline, a 2 at six months after treatment with AVR-RD-01 and a one at 12 months post-treatment with AVR-RD-01. The second patient in the Phase 2 trial, whose cardiac variant phenotype does not typically result in Gb3 accumulation in the kidney and skin, scored a zero at baseline and at six months post-treatment with AVR-RD-01. The third patient in the Phase 2 trial scored a 2 at baseline and a 2 at six months post-treatment with AVR-RD-01.

Vector Copy Number

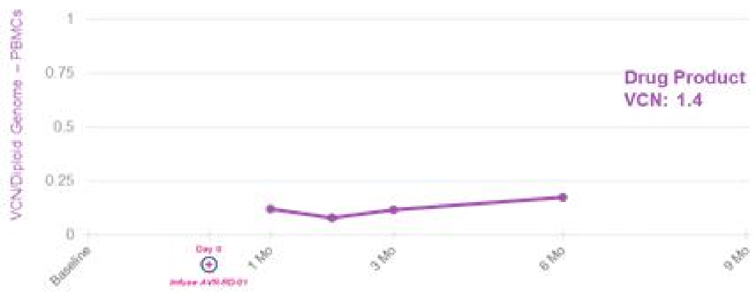
The first three patients in our Phase 2 clinical trial have exhibited consistent VCN trends following administration of AVR-RD-01. The graph below presents the VCN data in the first three patients of our Phase 2 clinical trial following dosing and at subsequent measurement points. For the fourth patient in our Phase 2 clinical trial of AVR-RD-01, who was dosed in December 2019 with our plato platform, nucleated blood cell VCN is not yet available. However, the VCN measurement of the drug product produced for this patient was 1.6.

Phase 2: Patient 1 Average VCN* in Nucleated Blood Cells post-AVR-RD-01 treatment

Phase 2: Patient 2 Average VCN* in Nucleated Blood Cells post-AVR-RD-01 treatment



Phase 2: Patient 3 Average VCN* in Nucleated Blood Cells post-AVR-RD-01 treatment



* Average VCN refers to the average number of copies of the lentiviral-vector inserted gene that are integrated into the genome of a cell, for a given cell population.

Kidney and Cardiac Function

Secondary endpoints of our Phase 2 trial include measurements of kidney function, as measured by estimated glomerular filtration rate, or eGFR, and measured glomerular filtration rate, or mGFR, as well as measures of cardiac function, as assessed by Left Ventricular Mass Index, or LVMI. eGFR is determined using the Chronic Kidney Disease Epidemiology Collaboration, or CKD-EPI, formula and mGFR is determined using plasma clearance of iohexol. The left ventricular mass, or LVM, is assessed by cardiac magnetic resonance imaging, or cardiac MRI, which is an imaging technology that enables non-invasive assessment of the function and structure of the heart. In general, for a patient with Fabry disease, an increase over time in LVM could potentially be expected. Improving patient outcomes by slowing or halting the progression of organ damage is a key mission of our Company and our investigational gene therapy programs. Interim data-to-date in the first two patients in our Phase 2 trial indicates kidney and cardiac functions have been stable and in the normal range at one year following administration of AVR-RD-01 investigational gene therapy. In the case of the first patient in our Phase 2 clinical trial, a 9.9% reduction in LVM was observed from baseline to one year post-treatment with AVR-RD-01. In the case of the second patient, a 1.7% increase in LVM was observed from baseline to one-year post-treatment.

Safety

Preliminary safety data from the ongoing Phase 2 study indicates that AVR-RD-01 was generally well-tolerated in all patients enrolled in the study.

As of the safety cut-off date of November 26, 2019, there were 98 non-serious AEs reported, none of which were deemed by the investigator to be possibly, probably, or definitely related to drug product. AEs in this study can be assigned to more than one causality assessment.

As of November 26, 2019, of the non-serious AEs, nine were related to study procedures, 50 were related to the medication used in the conditioning regimen, one was related to G-CSF/plerixafor, 16 were related to an underlying disease, and 22 were related to other causes.

As of November 26, 2019, four SAEs were reported, one pre-treatment and three post-treatment. No events were related to AVR-RD-01, and two events were related to the conditioning regimen. A fifth SAE, which was not related to AVR-RD-01, was reported for the fourth patient in the Phase 2 clinical trial, who was dosed after the safety cut-off date of November 26, 2019. Because this clinical trial is ongoing, safety data are preliminary and subject to change.

After beginning stem cell mobilization but prior to undergoing the conditioning regimen and treatment with AVR-RD-01, the first patient experienced a seizure, which is categorized as an SAE but unrelated to the study drug, conditioning regimen or stem cell mobilization. This event has resolved in the patient. In addition, during a scheduled protocol visit seven days after dosing, the same patient reported nausea and vomiting and was admitted to hospital for fluid hydration. Because the nausea and vomiting warranted hospital admission, the event was categorized as an SAE, possibly related to the conditioning regimen; nausea and vomiting have resolved in the patient. The treating physician decided to monitor the patient in hospital until the patient’s neutrophil count increased. Neutrophil and platelet counts recovered after dosing. On June 20, 2018, the patient was discharged from the hospital six days after admission and 13 days after transplant. Nausea, vomiting and dehydration resolved as of June 15, 2018. In the opinion of the investigator, the event was unrelated to the study drug or stem cell mobilization, but was deemed probably related to the conditioning regimen.

The second patient experienced a post-treatment SAE of drug-induced dermatosis seven days post-dosing. The rash was described as small, raised red bumps and were not painful. The patient was treated with hydrocortisone cream, and the rash resolved as of December 26, 2018. The patient was discharged from the hospital in less than 24 hours. In the opinion of the investigator, the relationship of the SAE to the procedure was not applicable and the relationship to stem cell mobilization, conditioning regimen and AVR-RD-01 was unknown.

An additional SAE of culture negative sepsis was reported in the second patient nine days after treatment on December 22, 2018. The patient was admitted to the hospital with a mild sore throat. His urine cultures were negative and his blood cultures were negative for both aerobic and anaerobic organisms. The patient was discharged from the hospital on the fourteenth day after transplant. In the opinion of the investigator, the relationship of the SAE to the conditioning regimen was definite and the relationship to stem cell mobilization and AVR-RD-01 was unrelated.

The fourth patient experienced a post-treatment SAE of non-neutropenic fever on January 25, 2020, 17 days post-dosing. The patient was admitted to the hospital with a sore throat, erythematous tonsillar pillars with slight exudate, and a temperature of 38.0°C. The patient was seen at the clinical site with improvement of mucositis and a normal temperature on January 13, 2020, twenty-five days post-treatment. In the opinion of the investigator, the relationship of the SAE to the conditioning regimen was possible and the relationship to stem cell mobilization and AVR-RD-01 was unrelated.

In addition to the above, each of the Phase 2 patients experienced a temporary suppression of absolute neutrophil counts and platelets, which is an expected consequence of the conditioning regimen.

AVR-RD-04, Our Gene Therapy for Cystinosis

Together with UCSD, we are developing CTNS-RD-04, which we refer to as AVR-RD-04, for the treatment of patients with cystinosis. AVR-RD-04 is manufactured from hematopoietic stem cells that are first harvested from the patient, modified to add the gene that encodes for cystinosin, and then infused into the patient. AVR-RD-04 is currently being studied by our collaborators at UCSD in a Phase 1/2 investigator-sponsored clinical trial. In October 2019 we announced that the first patient had been dosed with AVR-RD-04, and in February 2020 we announced initial clinical data for that patient.

Disease Overview

Cystinosis is a rare, genetic, autosomal recessive, lysosomal disease caused by the accumulation of the amino acid cystine that is produced in the lysosomes of cells as the result of protein degradation. Cystine is normally transported through the lysosomal membrane to the cytosol where it is reutilized after its transformation to cysteine. In cystinosis, cystine accumulates inside the lysosomes because of a defect in the gene that encodes cystinosin, a protein that transports cystine across the lysosomal membrane. Cystine is poorly soluble and forms crystals as its concentration increases. These crystals build up and cause complications in many organs and tissues. The kidneys and eyes are especially vulnerable to damage, and the muscles, thyroid, pancreas and testes may also be affected.

The most severe form of cystinosis begins in infancy, causing poor growth and a particular type of kidney damage in which certain molecules, such as glucose, amino acids, phosphate, and bicarbonate, that should be reabsorbed into the bloodstream are instead eliminated in the urine. These renal problems ultimately lead to impaired growth and may result in soft, bowed bones, especially in the legs. By the time the patient is approximately two years old, cystine crystals may be present in the cornea, and the buildup of these crystals in the eye causes pain and an increased sensitivity to light. Untreated children with cystinosis may experience complete kidney failure by the age of ten. Other signs and symptoms that may occur in untreated patients, especially after adolescence, include muscle deterioration, blindness, inability to swallow, diabetes, thyroid and nervous system problems. More than 90% of untreated patients require a kidney transplant before the age of 20. It is estimated that cystinosis disease is diagnosed in approximately one in 170,000 people.

Limitations of Current Therapies

Cystinosis is currently treated with two oral formulations of cysteamine that enter the lysosome and stimulate the breakdown of cystine into products that do not require the cystinosin protein to be transported. Oral treatment can delay the development of kidney failure by six to ten years if it is started at a very early age, however it cannot prevent kidney failure or the development of other complications, such as the formation of cystine crystals in the cornea. The approved oral therapies for cystinosis are Procysbi (delayed release cysteamine bitartrate), marketed by Horizon Orphan and Cystagon (cysteamine bitartrate) marketed by Mylan and Recordati S.p.A. In 2019, Procysbi generated worldwide net sales of approximately $162 million. The annual average cost to the healthcare system per patient prescribed Procysbi in the United States is between approximately $625,000 and $750,000.

Procysbi and Cystagon must be taken orally every 12 or six hours, respectively, leading to significant pill burden and compliance challenges. Because cysteamine works by directly binding to cystine, rather than through a typical small molecule that inhibits an enzyme or receptor, a substantial quantity is required. For adults, this can mean taking at least 12 capsules twice a day, every day. Oral therapy with cysteamine is associated with a high degree of noncompliance due to the frequency with which it must be dosed and the accompanying nausea, as well as the acrid sulfur smell that it produces in the breath and body. It has been estimated that only one third of patients are able to adhere to the strict dosing schedule. Studies have shown that adherence diminishes over time in adolescents and adults despite disease impact. Further, oral cysteamine treatment has no effect on ocular cystine crystals deposits, thus requiring patients to be treated with topical cysteamine eye drops which must be applied each hour the patient is awake.

Our Solution

We are developing AVR-RD-04 to potentially cure patients with cystinosis with a single dose of the patient's own hematopoietic stem cells modified in an *ex vivo* procedure. AVR-RD-04 is a lentiviral-based gene therapy containing a human gene for cystinosin designed to maximize the likelihood of sustained cystinosin production in hematopoietic stem cells and their progeny.

Ongoing Phase 1/2 Clinical Trial

In the Phase 1/2 clinical trial of AVR-RD-04 that is being conducted by our collaborators at UCSD, six patients with cystinosis who are currently being treated with cysteamine will be enrolled. The clinical trial's primary endpoints are safety and tolerability, assessed for up to two years after treatment, as well as preliminary efficacy as measured by changes in cystine levels in granulocytes. Secondary endpoints to assess preliminary efficacy include change from baseline in cystine levels in rectal mucosa as well as cystine crystal counts in the cornea and skin. These secondary efficacy endpoints will also be evaluated through clinical tests of kidney function, ophthalmologic measures, muscle strength, pulmonary function and neurological and psychometric function, as well as through patient-reported outcomes and assessments of health-related quality of life. The study drug utilized in this trial will not be manufactured using our plato platform, and neither the automated, closed manufacturing system nor LV2 will be used in connection with this investigator-sponsored clinical trial.

In February 2020, we announced initial clinical data for the first patient in the clinical trial of AVR-RD-04.

Vector Copy Number and Granulocyte Cystine Levels

The first patient in the Phase 1/2 clinical trial exhibited a VCN of 2.0 three months post-treatment with AVR-RD-04. VCN, which is expressed as VCN per diploid genome, refers to the average number of copies of the lentiviral-vector inserted gene that are integrated into the genome of a cell and is another measure that can be used to help assess the durability of a gene therapy. We believe that different diseases may require varying levels of VCN based on the underlying condition, and therefore VCN measurements across different diseases should be assessed separately.

One of the primary endpoints of the Phase 1/2 clinical trial is the change in the average level of cystine in granulocytes from baseline to up to two years post-treatment with AVR-RD-04. The first patient in the Phase 1/2 clinical trial exhibited granulocyte cystine levels of 1.5 nmol half cystine per milligram three months post-treatment with AVR-RD-04 as compared to the baseline value of 7.8. The patient's baseline value was measured two weeks after discontinuation of cysteamine treatment and prior to initiating mobilization. As the Phase 1/2 clinical trial progresses, we expect to identify clinically meaningful measures, such as renal function, polyuria and crystal levels in the cornea and photophobia.

Secondary Endpoints

Secondary endpoints of the Phase 1/2 clinical trial include measurements of kidney function and levels of cystine in the skin. These endpoints are not a comprehensive set of the secondary endpoints in the Phase 1/2 clinical trial and only reflect the data available to us as of three months following treatment with AVR-RD-04.

Assessment of kidney function includes measurements of eGFR and serum creatinine, or sCR. eGFR is determined using the CKD-EPI formula and sCR is measured as part of the comprehensive metabolic panel. The first patient in the Phase 1/2 clinical trial exhibited an sCR value of 2.1 mg/dL three months post-treatment with AVR-RD-04 as compared to a baseline value of 2.2 mg/dL, and an eGFR value of 40 mL/min/1.73m^2 three months post-treatment as compared to a baseline value of 38 mL/min/1.73m^2.

Levels of cystine in the skin are measured with *in vivo* confocal microscopy, or IVCM, on two separate areas of the skin: behind the ear and in a location determined by the treating physician. The two measurements are analyzed and quantified with 3D Image-Pro software and averaged. The first patient in the Phase 1/2 clinical trial exhibited a 32% reduction from baseline in skin cystine levels measured three months post-treatment with AVR-RD-04. The baseline measurement and three month data were obtained using IVCM. In addition, levels of cystine crystals in the skin will be measured using optical coherence tomography. These various skin measurements are considered experimental methodologies and will require additional study to determine their validity and significance.

Other Measurements

24-hour urine volume is measured by the total volume of urine produced in a 24-hour period as compared to a baseline 24-hour measurement taken prior to administration of AVR-RD-04. We believe this measurement may be suggestive of change in kidney function. At three months post-treatment with AVR-RD-04, the first patient in the Phase 1/2 clinical trial exhibited a 37% reduction from baseline in 24-hour urine volume.

Safety

As of the safety cut-off date of January 27, 2020, interim clinical data for the first patient dosed in the Phase 1/2 clinical trial appear to indicate that the AVR-RD-04 investigational gene therapy has been generally well tolerated with no unexpected safety events identified. No SAEs were reported as of the safety data cut-off date of January 27, 2020. A total of 22 AEs were reported as of the safety cut-off date of January 27, 2020, nine of which were moderate and 13 of which were mild. All reported AEs were consistent with expectations for the underlying disease and conditioning regimen prescribed by the study protocol. There have been no reports of safety events attributed to the AVR-RD-04 drug product.

AVR-RD-02, Our Gene Therapy for Gaucher Disease

We are developing AVR-RD-02 for the treatment of Type 1 Gaucher disease. We plan to manufacture AVR-RD-02 from hematopoietic stem cells that are first harvested from the patient, modified to add the gene that encodes for glucocerebrosidase, or GCase, and then infused into the patient. Patient enrollment has commenced for the Phase 1/2 clinical trial of AVR-RD-02 in patients with Type 1 Gaucher disease, and we expect to dose the first patient in the second quarter of 2020. In January 2020, we announced that we received notice of clearance from the FDA regarding an IND application for AVR-RD-02. This announcement followed receipt of FDA orphan drug designation status for AVR-RD-02 and enables us to expand the Phase 1/2 clinical trial in Gaucher disease to the United States, supported by our plato platform. The Phase 1/2 clinical trial for AVR-RD-02 is actively recruiting in Australia and Canada, with additional sites planned in the United States.

Disease Overview

Gaucher disease is a rare, autosomal recessive, lysosomal disease caused by a hereditary deficiency of functional GCase, an enzyme responsible for degrading glucocerebroside, a cell membrane building block, into glucose and lipids within lysosomes of cells. In patients with Gaucher disease, the recycling of glucocerebroside from the breakdown of old red and white blood cells is inhibited, leading to its accumulation in macrophages. These abnormal macrophages, known as Gaucher cells, accumulate in multiple organs, particularly the liver, spleen and bone marrow.

Gaucher disease is one of the most common lysosomal diseases. It is diagnosed in approximately one in 44,000 births worldwide and is more prevalent in certain ethnic groups, such as people of Ashkenazi Jewish heritage. Approximately 90% of patients suffering from Gaucher disease in western countries have Type 1 Gaucher disease, which manifests as multiple morbidities including enlargement of the spleen and liver, low red blood cells, or anemia, low platelet count, or thrombocytopenia, and bone abnormalities including bone pain, fractures and arthritis. Bruising, risk of bleeding and fatigue are common due to the thrombocytopenia and anemia. Compared with the general population, patients with Type 1 Gaucher disease have an approximately 20-fold increased risk of developing Parkinson’s disease. Type 1 Gaucher disease does not have manifestations of central nervous system symptoms.

Limitations of Current Therapies

Type 1 Gaucher disease is currently treated with bi-weekly infusions of ERT consisting of recombinant GCase over a patient's lifetime. The most commonly prescribed ERTs for Gaucher disease are Cerezyme, marketed by Sanofi Genzyme, and VPRIV, marketed by Shire.

Although long-term ERT for Gaucher disease results in some therapeutic benefit, ERTs leave patients with significant unmet needs. Twenty-five percent of patients with Gaucher disease continue to experience physical limitations following two years of ERT, and a clinically significant percentage of patients continue to experience bone pain, thrombocytopenia and enlargement of spleen following ten years of ERT. In a published study of ERT therapy for Gaucher disease, six target goals were evaluated, including parameters for hemoglobin and platelet levels, spleen and liver volumes, and general bone pain and severe disabling bone pain known as bone crisis. Following at least four years of ERT in this study, approximately 60% of patients failed to achieve one or more of these six target goals.

In addition to ERTs, the FDA has approved several oral therapies for the treatment of Gaucher disease, including Zavesca (miglustat) marketed by Actelion and Cerdelga (eliglustat) marketed by Sanofi Genzyme. We believe these oral therapies also provide suboptimal treatment. Zavesca is approved as a second line therapy and is associated with significant toxicities, including diarrhea, weight loss and tremors. Cerdelga is not approved for use in children, has highly variable metabolism due to patient-to-patient genetic variations and is highly susceptible to interactions with other drugs.

Both ERTs and oral therapies for Gaucher impose significant costs on the healthcare system. In the United States, the annual average cost to the healthcare system per patient prescribed Cerezyme or VPRIV is between approximately $325,000 and $400,000. The annual average cost to the healthcare system per patient prescribed Cerdelga is approximately $262,500. In 2019, Sanofi Genzyme's Cerezyme and Cerdelga together generated worldwide net sales of €914 million euros and Takeda's VPRIV generated worldwide net sales of approximately ¥37.1 billion Japanese yen.

Our Solution

We are developing AVR-RD-02 to potentially cure patients with Type 1 Gaucher disease with a single dose of the patient's own hematopoietic stem cells modified in an *ex vivo* procedure. AVR-RD-02 is a lentiviral-based gene therapy that contains a codon-optimized human gene and is designed to maximize the likelihood of sustained GCase production in hematopoietic stem cells and their progeny.

Phase 1/2 Clinical Trial

We have initiated a Phase 1/2 clinical trial of AVR-RD-02 in patients with Type 1 Gaucher disease. Patient enrollment has commenced in the Phase 1/2 clinical trial, and we expect to dose the first patient in the second quarter of 2020. This clinical trial is actively recruiting in Australia and Canada, with additional sites planned in the United States. Our initial clinical trial will be an adaptive trial that will include both treatment-naïve patients and patients that are currently stable on ERT. We intend to enroll eight to 16 patients, between the ages of 16 and 35, with Type 1 Gaucher disease. Patients currently prescribed ERT will cease treatment throughout the clinical trial. All enrolled patients will receive a single treatment with AVR-RD-02 and will be followed for 52 weeks to measure safety and efficacy. We intend to utilize our plato platform for all patients enrolling in our Phase 1/2 clinical trial of AVR-RD-02. Our efficacy endpoints for this clinical trial will include measures of clinical efficacy, such as liver and spleen volumes, hemoglobin, platelet counts, bone pain and bone density measures along with other blood markers used in Gaucher disease.

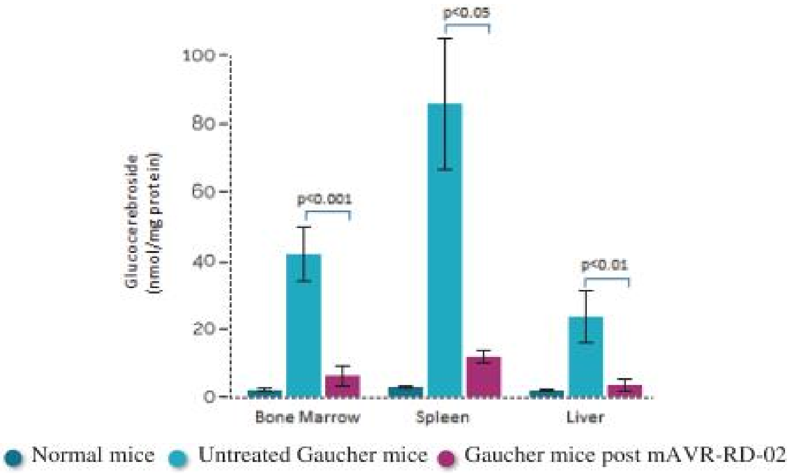
Preclinical Data

AVR-RD-02 is based on extensive preclinical work from our collaborators at Lund University and leverages findings published in 2015 in *Molecular Therapy* which concluded that, in a Gaucher disease mouse model, a lentiviral-based gene therapy containing the gene for GCase could prevent the development and reverse clinically relevant signs of the disease.

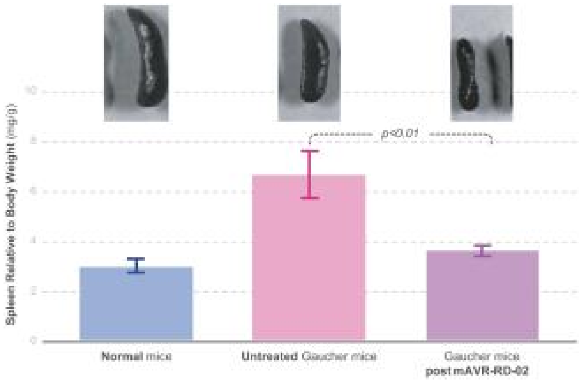
In preclinical studies, a mouse model of Type I Gaucher disease exhibited increased glucocerebroside levels in the clinically-relevant tissues, the bone marrow, spleen and liver, and mimicked many of the same symptoms seen in patients such as an enlarged spleen. These preclinical studies assessed glucocerebroside levels, Gaucher cell infiltration, and spleen volume in the mouse model over 20 weeks following treatment with mouse bone marrow cells transduced with the clinical vector, which we refer to as mAVR-RD-02. The vector used in this preclinical study of mAVR-RD-02 was an academic vector of similar design to LV2, but also included a marker gene to enable tracking of the transduced cells *in vivo*. This marker gene was removed as it is not required in the clinic, and the transgene encoding functional glucocerebrosidase was inserted into the LV2 backbone.

When mice with established disease were treated with mAVR-RD-02, glucocerebroside levels decreased and symptoms such as an enlarged spleen were reversed within 20 weeks. Over this period, increased enzyme levels were observed in the bone marrow, spleen and liver in the mouse model. In addition, the mice that were treated with mAVR-RD-02 prior to manifesting symptoms did not develop symptoms of the disease. We believe these data support the potential efficacy of AVR-RD-02 to prevent, as well as reverse, symptoms in patients with Gaucher disease.

mAVR-RD-02 Leads to a Significant Reduction in Glucocerebroside Levels Across Multiple Clinically-relevant Tissues



Ex Vivo **Lentiviral-based Gene Therapy Leads to a Significant Reduction in Spleen Volume in a Mouse Model of Gaucher Disease**



AVR-RD-03, Our Gene Therapy for Pompe Disease

We are developing AVR-RD-03 for the treatment of Pompe disease. We will manufacture AVR-RD-03 from hematopoietic stem cells that are first harvested from the patient, modified to add the gene that encodes for acid alpha glucosidase A, or GAA, attached to a peptide sequence known as a glycosylation-independent lysosomal targeting, or GILT, tag and then infused into the patient. AVR-RD-03 will incorporate a GILT tag because the GILT tag has been found to increase the uptake of GAA into cells, especially in muscle cells by a multiple of 25, which is a particularly important target tissue for patients with Pompe disease and a target tissue that is considered difficult to access for ERT. AVR-RD-03 is designed to incorporate a potent promoter to increase volume of system enzyme in circulation.

Disease Overview

Pompe disease is a rare, autosomal recessive lysosomal disease caused by a mutation in the gene that encodes for GAA that results in the buildup of glycogen, a complex sugar, in the body's cells. The accumulation of glycogen in certain organs and tissues, especially muscles, impairs normal tissue and organ function. Patients with Pompe disease experience serious muscle related problems, including progressive muscle weakness, especially in the legs and trunk, and the muscles that control breathing. As the disorder progresses, breathing problems can lead to respiratory failure.

The overall diagnosed incidence of Pompe disease is estimated to be approximately one in 58,000 people although frequency and disease progression varies with age of onset, ethnicity and geography. Overall diagnosed incidence of Pompe disease is projected to increase to one in 22,000 people as it is increasingly included in newborn screening panels.

The severity of Pompe disease symptoms and rate of progression is highly variable and correlated with age of symptom onset and the degree of enzyme deficiency. Infantile or early onset disease, the most severe form of Pompe disease, accounts for approximately 25% of all affected patients. Those with early-onset disease are usually diagnosed in the first few months of life and is associated with cardiomyopathy. Left untreated, these patients can die due to heart failure, respiratory distress or malnutrition resulting from feeding difficulties within the first year of life. Patients with late-onset disease typically have higher enzyme levels and usually have symptoms such as reduced mobility and respiratory problems but are not at increased risk of developing cardiomyopathy. Late-onset patients experience progressive difficulty walking and respiratory decline. While life expectancy can vary, Pompe disease is a life-limiting disease that can result in death due to complications from respiratory failure.

Limitations of Current Therapies

Pompe disease is currently treated with ERT delivered by bi-weekly intravenous infusion. The only approved therapy for Pompe disease is Lumizyme (known as Myozyme outside of the United States), marketed by Sanofi Genzyme, which generated worldwide net sales of €918 million euros in 2019. The annual average cost to the healthcare system per patient prescribed Lumizyme in the United States is approximately $500,000.

Though patients treated with ERT for Pompe disease have improved survival and respiratory function, ERT is not curative, and patients in long-term observational studies continue to have increased risk of heart failure and have residual muscle weakness including difficulties swallowing with risk of aspiration. One challenge with ERT treatment for Pompe disease is that a standard dose requires approximately twenty-fold more enzyme compared to standard doses for Fabry or Gaucher diseases. Large doses of Lumizyme that are delivered systemically in order to achieve potentially therapeutic levels in the target tissues result in approximately 90% of patients developing antibodies against the therapy. These antibody responses may impact both the efficacy and safety of Lumizyme. The FDA approval of Lumizyme carries a black box warning related to the risk of severe allergic and immune mediated reactions, including life-threatening anaphylaxis.

Our Solution

We are currently conducting IND-enabling preclinical studies of AVR-RD-03 to potentially cure patients with late-onset Pompe disease. We are developing AVR-RD-03 to be a gene therapy product containing a codon-optimized human gene for GAA attached to a GILT tag designed to increase uptake of GAA in muscle cells. AVR-RD-03 will target patients with late onset Pompe disease, which represent the majority of patients with this disease. In addition, we believe that the utilization of busulfan in our conditioning regimen may have the potential to allow AVR-RD-03 to cross the blood-brain barrier, a feature which may yield therapeutic benefit.

Preclinical Data

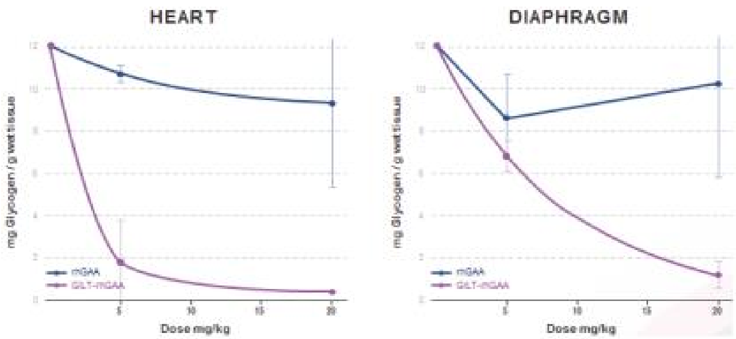
Published preclinical results from a mouse model of Pompe disease support the potential of lentiviral-based gene expression of GAA to prevent some of the symptoms of GAA deficiency. These results also demonstrated the need to further increase the uptake of GAA into muscle cells to treat patients, which is a known challenge for ERTs and leads to the use of large quantities of enzyme to attempt to deliver effective treatment levels.

In these published preclinical results from a mouse model of Pompe disease, treatment utilizing a lentiviral vector encoding GAA led to increased levels of active enzyme across multiple organs and tissues, including clinically relevant tissues such as the heart and diaphragm. This enzyme activity was correlated with reductions in glycogen storage in these tissues. While reduction in left ventricular mass and normalization of heart rate were observed in the mouse models seven to eight months following treatment with this lentiviral-based gene expression of GAA, only lesser improvements in other muscles, such as skeletal muscle strength, were observed.

We believe we can use a GILT tag to address the known challenges of skeletal muscle uptake in patients with Pompe disease. Attachment of a GILT tag to a particular protein can increase the effective uptake of that protein into target tissues. We are designing AVR-RD-03 to use a GILT tag to facilitate GAA uptake into cells and thereby reduce the therapeutically required amount of GAA produced by a patient's cells following gene therapy treatment.

In mouse models of Pompe, administration of recombinant GAA with the GILT tag demonstrated significant reduction in glycogen in cardiac and skeletal muscles as compared to the administration of recombinant GAA alone. We licensed GILT tag technology from BioMarin and are incorporating a GILT tag into our lentiviral vector with the goal of the patient producing GILT-tagged GAA following treatment with AVR-RD-03.

GILT-tag Version of Recombinant Human (rh)GAA Impact on Levels of Stored Glycogen Compared to non GILT-tagged Recombinant Human (rh)GAA



Manufacturing

Industrializing Our Gene Therapies Through Our Outsourced Manufacture and Supply Network

We are establishing global manufacturing relationships that we believe will provide us with drug product manufacturing capabilities to support all aspects of the development and eventual commercialization of our gene therapies. Our team has leveraged their broad expertise in the manufacturing of gene and cellular therapies to build a global network of CMO partners for the development and manufacture of drug products and outsourced suppliers for the supply of vectors and plasmids. We believe that our third-party CMO partners and suppliers have capacity to accommodate current and future clinical trials and we are continuing to build a global network that we expect will have capacity to generate sufficient quantities to meet our expected commercial needs.

To optimize production of our gene therapies, we have moved our cell processing to an automated, closed system using disposable supplies. We believe this industrialized manufacturing process will enable a repeatable approach through which we can design and manufacture commercially viable lentiviral gene therapies to potentially treat a large variety of genetic disorders. We expect that our automation of the manufacturing processes will further increase our CMO partners' manufacturing capacity.

Producing a Patient's Gene Therapy

We start the process to produce a patient's gene therapy with the mobilization of a patient's stem cells from the bone marrow to the blood stream and isolate them using a standard procedure used in stem cell transplants. We then treat these cells with a lentiviral vector to insert the equivalent of a functional copy of the gene that is defective in the target disease in a 48-hour process. We preserve patients' modified cells at a very low temperature, using cryopreservation to maintain the cellular material in optimal condition until it is thawed prior to being infused into the patient. The cryopreservation allows us to conduct a number of tests to validate the modified cells prior to introducing them into the patient. We believe cryopreservation will also enable us to supply our products globally, as well as significantly increase the convenience of infusion scheduling for clinicians and patients, compared to fresh *ex vivo* gene therapy products that may have shelf-lives of only 24 hours.

Prior to infusion of the gene therapy-modified cells into the patient, the patients undergo a conditioning regimen to remove some of the patient's unmodified cells from the bone marrow to create sufficient space for the modified hematopoietic stem cells to engraft and produce their progeny. The conditioning regimen used in our approach for AVR-RD-01, AVR-RD-02 and AVR-RD-03 may be administered in either an inpatient or an outpatient treatment setting on a case-by-case basis as may be directed by the patient's physician.

After the conditioning regimen is complete, the lentivirally-modified stem cells are infused into the patient by intravenous administration in an outpatient setting. After infusion, these cells engraft into the bone marrow, replicate and differentiate into all the various types of blood cells that will distribute throughout the body. These widely distributed cells lead to sustained expression of the desired therapeutic enzyme or other protein. The sustained expression of the functional enzyme is a direct substitute for the protein currently delivered by ERTs, which require periodic infusions.

Intellectual Property and Other Barriers to Entry

The proprietary nature of, or protection for, our gene therapy technology, our product candidates, our production methods and supply chain are an important part of our strategy to develop and commercialize novel therapies. To maximize the commercial opportunity for our gene therapies, if approved, we and our partners have been building and continue to build barriers to entry by our competitors, including:

- We in-license and develop know-how, including data, relating to certain of our product candidates.
- We rely on trade secret protection to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.
- Our management team has significant experience in cell processing and commercial-scale cellular therapy manufacturing. Leveraging this experience, we are building our global network of suppliers and CMO partners which combines their expertise in vector manufacturing with a closed, automated manufacturing system, all utilizing CGMP.
- Our gene therapies are designed to potentially provide a curative benefit. If our gene therapies are approved before any other potentially curative treatments, we believe the benefits of our approach and the resulting first mover advantage may provide meaningful disincentive for companies seeking to develop potentially curative therapies that may compete with our own. See "—Competition."
- We are developing therapies to treat rare diseases and expect to pursue orphan-drug designation in the United States and similar protection outside of the United States. To date, we have received from the FDA orphan-drug designation for AVR-RD-01 for the treatment of Fabry disease, AVR-RD-04 for the treatment of cystinosis, and AVR-RD-02 for the treatment of Gaucher disease. These and other regulatory exclusivities, if granted or applicable, can prevent competitors, during the exclusivity period, from obtaining regulatory approval of the same drug or biological product for the same indication. See "—Government Regulation."
- We currently in-license, and we expect to file our own, patents and patent applications relating to certain of our product candidates.

We have in-licensed patents and patent applications from BioMarin Pharmaceutical Inc. and GenStem Therapeutics, Inc. directed to compositions and methods related to the manufacture and use of certain of our gene therapies. In addition, we have in-licensed certain intellectual property rights and know-how from the University Health Network and affiliates of Lund University. For example, we have in-licensed know-how and data related to AVR-RD-01, including certain information about the vector and its use, from University Health Network, and we have in-licensed know-how and data related to AVR-RD-02, including certain information about the vector and its use, from certain academic scientists affiliated with Lund University. Each of our licenses are limited to particular fields, such as Fabry disease, Gaucher disease, Pompe disease, or cystinosis, and are subject to certain retained rights. We do not control the prosecution and maintenance of all of our in-licensed patents and patent applications, and our rights to enforce the patents are limited in certain ways. For additional detail regarding the risks associated with our license agreements see "Risk Factors—Risks Related to Intellectual Property."

As of March 6, 2020, our in-licensed patent portfolio relating to certain of our gene therapies included the following:

- *AVR-RD-03*: two U.S. patents, projected to expire in 2022 and 2023, and two U.S. patent applications, which if granted, would be projected to expire in 2022 and 2029, as well as corresponding patents and patent applications in certain foreign jurisdictions, as they pertain to compositions and methods for promoting lysosomal uptake of acid alpha-glucosidase and the treatment of Pompe disease. These patents and patent applications are licensed to us by BioMarin and relate to the GILT tag; and
- *AVR-RD-04*: one U.S. patent application, which, if granted, would be projected to expire in 2038, as well as corresponding patents and patent applications in certain foreign jurisdictions, containing claims directed to hematopoietic stem cells expressing cystinosin and methods of using the same for the treatment of cystinosis. These patent applications are licensed to us by GenStem Therapeutics, and GenStem obtained its rights from the University of California, San Diego.

The term of any given patent depends upon the legal term of patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the application, subject to the timely payment of maintenance fees, among other considerations. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office, or USPTO, in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed commonly owned patent. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a result of FDA regulatory review period. However, the restoration period cannot be longer than five years and the total patent term including the restoration period must not exceed 14 years following FDA approval. In certain foreign jurisdictions similar extensions as compensation for regulatory delays are also available. The actual protection afforded by a patent varies on a claim by claim and country by country basis for each applicable product and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent. Currently, we do not own or license patents or patent applications related to our AVR-RD-01 or AVR-RD-02 product candidates. We rely, in some circumstances, on trade secrets and unpatented know-how that is either owned by or licensed to us to protect our technology. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors.

License Agreements

Exclusive License Agreement with University Health Network

In November 2016, we entered into a license agreement with University Health Network, or UHN, pursuant to which UHN granted us an exclusive worldwide license under certain intellectual property rights and a non-exclusive worldwide license under certain know-how, including certain rights to data, in each case subject to certain retained rights, to develop, commercialize and sell products for use in the treatment of Fabry disease. Intellectual property licensed to us under this agreement relates to our Fabry program. In addition, for three years following the execution of the agreement, UHN granted us an exclusive option to obtain an exclusive license under certain improvements to the licensed intellectual property rights as well as an exclusive option to negotiate a license under certain other improvements. Under the terms of the agreement, we are required to meet certain performance milestones within specified timeframes. UHN may terminate the agreement if we fail to meet these performance milestones despite using commercially reasonable efforts and we are unable to reach agreement with UHN on revised timeframes.

As consideration for the licenses, we paid to UHN a one-time upfront fee in the amount of C$75,000 and are obligated to pay an additional annual fee until the first sale of a licensed product in certain markets. We are also required to make payments to UHN in connection with the achievement of certain development and regulatory milestones, in an aggregate amount of C$2.45 million, as well as royalties on a country-by-country basis of a low to mid-single digit percentages on annual sales of licensed products and a lower single digit royalty in certain circumstances. Additionally, we will pay a low double-digit percentage of all sublicensing revenue. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration or termination of the last valid claim under the licensed patent rights in such country (if and when any such patent rights come into existence under the license agreement in the future), the tenth anniversary of the first commercial sale of such licensed product in such country and the expiration of any applicable regulatory exclusivity in such country.

In addition, under this agreement we made a philanthropic commitment to donate funds to organizations for the benefit of the Canadian Fabry community in an amount equal to a low double-digit percentage of our royalty payments and regulatory milestone payments, up to a maximum amount of C$500,000 in any calendar year.

Unless terminated earlier, this exclusive license agreement with UHN will expire upon the expiration of our royalty obligation for all licensed products. Either we or UHN may terminate the license agreement if the other party commits a material breach and fails to cure such breach within a certain period of time. UHN may terminate this agreement if we enter into bankruptcy or insolvency. We may terminate this agreement for any reason upon notice to UHN.

License Agreement with Lund University Rights Holders

In January 2017, we entered into an exclusive license agreement with Prof. Stefan Karlsson and Dr. Maria Dahl, affiliates of Lund University, pursuant to which Prof. Karlsson and Dr. Dahl, and certain other relevant rights holders that may have an interest in intellectual property generated under a research project we are funding with Lund University, granted to us an exclusive worldwide license, subject to certain retained rights, under certain intellectual property rights to develop, commercialize and sell products in any and all uses relevant to Gaucher disease. Intellectual property licensed to us under this agreement relates to our Gaucher program.

As consideration for the license, we are required to make payments in connection with the achievement of certain milestones up to an aggregate of $550,000.

Our license agreement with the rights holders expires on the latest of (i) the twentieth anniversary of the end of a certain research project we are funding pursuant to an agreement with Lund University, (ii) the expiration of the term of any patent filed on the licensed rights that covers a licensed product, (iii) the expiration of any applicable marketing exclusivity right and (iv) such time that neither we nor any of our sublicensees or partners or contractors are commercializing a licensed product. Either we or the rights holders acting together may terminate the license agreement if the other such party commits a material breach and fails to cure such breach within a certain period of time, or if the other party enters into liquidation, becomes insolvent, or enters into composition or statutory reorganization proceedings.

License Agreement with BioMarin Pharmaceutical Inc.

In August 2017, we entered into a license agreement with BioMarin Pharmaceutical Inc., or BioMarin, pursuant to which BioMarin granted us an exclusive worldwide license under certain intellectual property rights related to GILT tags owned or controlled by BioMarin to develop, commercialize and sell retroviridae-based gene therapy products for use in the treatment of Pompe disease. This agreement was amended in February 2018 and again in January 2020 to, among things, provide that BioMarin would supply us with certain materials related to the GILT tags technology. Under the terms of the agreement, we must use commercially reasonable efforts to develop and commercialize one or more licensed products in the United States and certain European countries. In addition, we are required to initiate an IND-enabling pharmacology/toxicology study of a licensed product within a specified period of time.

As consideration for the license, we paid an initial license fee in the amount of $500,000 and issued 233,765 shares of our Series B preferred stock to BioMarin at the time of our Series B financing. We are also obligated to make payments to BioMarin upon achievement of certain milestones up to an aggregate of $13 million and pay to BioMarin a low single digit royalty percentage on net sales of licensed products covered by patent rights in a relevant country. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration or termination of the last valid claim under the licensed patent rights in such country, which is currently projected to occur in 2029, the tenth anniversary of the first commercial sale of such licensed product in such country and the expiration of any applicable regulatory exclusivity in such country.

Unless terminated earlier, our license agreement with BioMarin will expire upon the expiration of our royalty obligation for all licensed products throughout the world. Either we or BioMarin may terminate the license agreement if the other party commits a material breach and fails to cure such breach within a certain period of time. BioMarin may also terminate the agreement in the event of any challenge or opposition to the licensed patent rights or related actions brought by us or our affiliates or sublicensees, or if we, our affiliates or sublicensees knowingly assist a third party in challenging or otherwise opposing the licensed patent rights, except as required under a court order or subpoena. In addition, BioMarin may terminate the agreement upon our bankruptcy or insolvency. We may terminate the agreement for any reason upon notice to BioMarin.

License Agreement with GenStem Therapeutics, Inc.

In October 2017, we entered into a license agreement with GenStem Therapeutics, Inc., or GenStem, pursuant to which GenStem granted us an exclusive worldwide license, subject to certain retained rights, under certain intellectual property rights owned or controlled by GenStem related to our cystinosis program, including certain rights licensed to GenStem from the University of California, San Diego, to develop, commercialize and sell products for use in the treatment of cystinosis. Under the terms of the agreement, we must use commercially reasonable efforts to develop and commercialize one or more licensed products in the United States and in at least one country from other specified markets. We also agreed to comply with certain access requirements consistent with the California Institute for Regenerative Medicine regulations and to manufacture certain licensed products substantially in the United States.

As consideration for the license, we paid an initial license fee in the amount of $1 million and are required to make payments upon completion of certain development milestones up to an aggregate of $16 million. For example, in November 2019 we made a $2 million payment in connection with the dosing of the first patient in the investigator-sponsored Phase 1/2 clinical trial of AVR-RD-04 in cystinosis in the United States. Additionally, we will pay to GenStem a tiered mid to high-single digit royalty percentage on annual net sales of licensed products as well as a low double-digit percentage of sublicense income received from certain third party sublicensees. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis on the eleventh anniversary of the first commercial sale of such licensed product in such country or the expiration of the last valid claim under the licensed patent rights covering such licensed product in such country, which is currently projected to occur in 2038, whichever is later.

Unless terminated earlier, our license agreement with GenStem will terminate upon the expiration of our royalty obligation for all licensed products throughout the world. Either we or GenStem may terminate the license agreement if the other party commits a material breach and fails to cure such breach within a certain period of time. In addition, we may terminate the agreement for any reason upon notice to GenStem.

Competition

Our industry is highly competitive and subject to rapid and significant technological change. Our potential competitors include larger pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as academic institutions, government agencies and private and public research institutions. Key competitive factors affecting the commercial success of our gene therapies are likely to be efficacy, safety and tolerability profile, reliability, convenience, price and reimbursement.

The market for treatment of lysosomal diseases is especially large and competitive. The gene therapies we are currently developing, if approved, will face competition.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a small number of our competitors. Accordingly, our competitors may be more successful than we may be in obtaining FDA approval for drugs and achieving widespread market acceptance. Our competitors' products may be more effective, or more effectively marketed and sold, than any product we may commercialize and may render our gene therapies obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our gene therapies. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. Finally, the development of new treatment methods for the diseases we are targeting could render our gene therapies non-competitive or obsolete. See "Risk Factors—Risks related to the discovery and development of our product candidates—We face significant competition and our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialize any of our product candidates," and elsewhere in this Annual Report on Form 10-K for more information regarding competitors and competitive products.

Government Regulation

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. Each clinical study protocol for a gene therapy product must be reviewed by the FDA and, in some instances, the National Institute of Health, or NIH, through its Recombinant DNA Advisory Committee, or RAC. FDA approval must be obtained before the marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the Center for Biologics Evaluation and Research, or CBER, regulates gene therapy products. The CBER works closely with the NIH and its RAC, which makes recommendations to the NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to proposed and ongoing gene therapy protocols. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in INDs for gene therapies.

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Biological Products Development Process

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical studies may begin;
- approval by an independent institutional review board, or IRB, or ethics committee at each clinical study site before each study may be initiated;
- performance of adequate and well-controlled human clinical studies according to the FDA’s regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a Biologics License Application, or BLA, for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical studies;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with CGMPs, to assure that the facilities, methods and controls are adequate to preserve the biological product’s identity, strength, quality and purity and, if applicable, the FDA’s current good tissue practices, or GTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA;
- payment of user fees for FDA review of the BLA (unless a fee waiver applies); and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. An IND is a request for authorization from the FDA to ship an unapproved, investigational product in interstate commerce and to administer it to humans, and must become effective before clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin. In addition to the submission of an IND to the FDA before initiation of a clinical trial in the United States, certain human clinical trials involving recombinant or synthetic nucleic acid molecules had historically been subject to review by the Recombinant DNA Advisory Committee, or RAC, of the National Institutes of Health, or NIH, Office of Biotechnology Activities, or the OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines. On August 17, 2018, the NIH issued a notice in the Federal Register and issued a public statement proposing changes to the oversight framework for gene therapy trials, including changes to the applicable NIH Guidelines to modify the roles and responsibilities of the RAC with respect to human clinical trials of gene therapy products, and requesting public comment on its proposed modifications. During the public comment period, which closed October 16, 2018, the NIH announced that it will no longer accept new human gene transfer protocols for review as a part of the protocol registration process or convene the RAC to review individual clinical protocols. In April 2019, NIH announced the updated guidelines, which reflect these proposed changes, and clarified that these trials will remain subject to the FDA's oversight and other clinical trial regulations, and oversight at the local level will continue as set forth in the NIH Guidelines. Specifically, under the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The FDA also may impose clinical holds on a biological product candidate at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

Clinical studies involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical studies are conducted under protocols detailing, among other things, the objectives of the clinical study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical study will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical studies must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical study must be reviewed and approved by an Institutional Review Board, or IRB, at or servicing each institution at which the clinical study will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical studies are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical study subject or his or her legal representative and must monitor the clinical study until completed. Clinical research involving recombinant DNA that is subject to NIH guidelines also must be reviewed by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

Clinical studies typically are conducted in three sequential phases that may overlap or be combined:

- *Phase 1*. The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- *Phase 2*. The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.
- *Phase 3*. Clinical studies are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical study sites. These clinical studies are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for approval and product labeling.

Post-approval clinical studies, sometimes referred to as Phase 4 clinical studies, may be conducted after initial marketing approval. These clinical studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical studies must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical studies may not be completed successfully within any specified period, if at all. The FDA or the sponsor, acting on its own or based on a recommendation from the sponsor's data safety monitoring board may suspend a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, efficacy, purity and potency of human gene therapy products, or that the data generated in these studies will be acceptable to the FDA to support marketing approval. The NIH has a publicly accessible database, the Genetic Modification Clinical Research Information System which includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these studies.

Concurrent with clinical studies, companies usually complete additional animal studies and also must develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with CGMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. Review and Approval Processes

After the completion of clinical studies of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. In most cases, the submission of a BLA is subject to a substantial application user fee, although the fee may be waived under certain circumstances. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, for original BLAs, the FDA has ten months from the filing date in which to complete its initial review of a standard application and respond to the applicant, and six months from the filing date for an application with priority review. The FDA does not always meet its PDUFA goal dates, and the review process is often significantly extended by FDA requests for additional information or clarification. This review typically takes twelve months from the date the BLA is submitted to the FDA because the FDA has approximately two months to make a ''filing'' decision. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with CGMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy, or REMS, is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA typically will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with CGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with GTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue-based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the GTP requirements is to ensure that cell and tissue-based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. To assure CGMP, GTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA for a novel product (e.g., new active ingredient, new indication, etc.) must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical studies are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical studies. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical studies, sometimes referred to as Phase 4 clinical studies, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting a BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor’s product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

Expedited Development and Review Programs

The FDA has various programs, including Fast Track designation, breakthrough therapy designation, accelerated approval and priority review, that are intended to expedite or simplify the process for the development and FDA review of drugs and biologics that are intended for the treatment of serious or life-threatening diseases or conditions. These programs do not change the standards for approval but may expedite the development or approval process. To be eligible for fast track designation, new drugs and biological products must be intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. One benefit of fast track designation, for example, is that the FDA may consider for review sections of the marketing application for a product that has received Fast Track designation on a rolling basis before the complete application is submitted.

Under the breakthrough therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible.

Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Under priority review, the FDA’s goal is to review an application in six months, compared to ten months for a standard review.

Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

Regenerative Medicine Advanced Therapies Designation

As part of the 21st Century Cures Act, enacted in December 2016, Congress amended the FD&C Act to facilitate an efficient development program for, and expedite review of regenerative medicine advanced therapies, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Regenerative medicine advanced therapies do not include those human cells, tissues, and cellular and tissue based products regulated solely under section 361 of the Public Health Service Act and 21 CFR Part 1271. This program is intended to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that the FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. The FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with the FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy with RMAT designation that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence from clinical studies, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. Like the FDA's other expedited development programs, RMAT designation does not change the standards for approval but may expedite the development or approval process.

Post-Approval Requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to CGMP. We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the CGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of CGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical holds, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors or other stakeholders, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with CGMPs and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain CGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. In addition, a patent can only be extended once and only for a single product. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our patents, if and as applicable, to add patent life beyond its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods, including some regulatory exclusivity periods tied to patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The ACA, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biological product is granted four and twelve year exclusivity periods from the time of first licensure of the product. FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product, and FDA will not approve an application for a biosimilar or interchangeable product based on the reference biological product until twelve years after the date of first licensure of the reference product. “First licensure” typically means the initial date the particular product at issue was licensed in the United States. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity, or potency. Therefore, one must determine whether a new product includes a modification to the structure of a previously licensed product that results in a change in safety, purity, or potency to assess whether the licensure of the new product is a first licensure that triggers its own period of exclusivity. Whether a subsequent application, if approved, warrants exclusivity as the “first licensure” of a biological product is determined on a case-by-case basis with data submitted by the sponsor.

Additional Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act, to which we are subject, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity.

Government Regulation outside of the United States

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies. In the European Union, for example, a Clinical Trial Application, or CTA, must be submitted for each clinical trial to each country’s national health authority and an independent ethics committee, much like the FDA and an IRB, respectively. Once the CTA is approved in accordance with a country’s requirements, the corresponding clinical study may proceed.

The requirements and process governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical studies must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational product under European Union regulatory systems, we must submit a marketing authorization application. The application used to file the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, region-specific document requirements. The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator’s data to assess a generic or biosimilar application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator’s data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the European Union’s regulatory authorities to be an innovative medicinal product, and products may not qualify for data exclusivity. Products receiving orphan designation in the European Union can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an “orphan medicinal product” in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- The second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- The applicant consents to a second orphan medicinal product application; or
- The applicant cannot supply enough orphan medicinal product.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical studies must be conducted in accordance with GCPs and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Other Healthcare Laws and Compliance Requirements

In addition to FDA restrictions on the marketing of pharmaceutical products, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our business or financial arrangements and relationships through which we market, sell and distribute the gene therapies for which we obtain approval. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity can be found guilty of violating the statute without actual knowledge of the statute or specific intent to violate it. In addition, a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act, or FCA. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution;

- federal civil and criminal false claims laws and civil monetary penalty laws, including the FCA, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment to, or approval by Medicare, Medicaid, or other federal healthcare programs, knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or an obligation to pay or transmit money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. The FCA also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery;

- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary’s selection of a particular supplier of items or services reimbursable by a federal or state governmental program;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;

- the federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program to report annually to the U.S. Department of Health and Human Services information related to payments or other transfers of value made to physicians (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;

- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws described above, among others, some of which may be broader in scope and may apply regardless of the payor. Many U.S. states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare services reimbursed by any source, not just governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America’s Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. There are ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement we could be subject to penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws.

Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including penalties, fines, imprisonment and/or exclusion or suspension from federal and state healthcare programs such as Medicare and Medicaid and debarment from contracting with the U.S. government. In addition, private individuals have the ability to bring actions on behalf of the U.S. government under the federal False Claims Act as well as under the false claims laws of several states.

Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices, including our arrangements with physicians and other healthcare providers, some of whom receive stock options as compensation for services provided, may not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, imprisonment, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our gene therapies outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

If any of the physicians or other healthcare providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs, which may also adversely affect our business.

Regulators globally are also imposing greater monetary fines for privacy violations. For example, in 2016, the European Union adopted a new regulation governing data practices and privacy called the General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. Non-compliance with the GDPR may result in monetary penalties of up to €20 million or 4% of worldwide revenue, whichever is higher. Notably, on January 21, 2019, Google was fined almost $57 million by French regulators for violating GDPR.

European Data Collection

The collection and use of personal health data in the European Union is governed by the provisions of the Data Protection Directive, and as of May 25, 2018 the GDPR. The GDPR applies to any company established in the European Union as well as to those outside the European Union if they collect and use personal data in connection with the offering of goods or services to individuals in the European Union or the monitoring of their behavior. The GDPR enhances data protection obligations for processors and controllers of personal data, including, for example, expanded disclosures about how personal information is to be used, limitations on retention of information, mandatory data breach notification requirements and onerous new obligations on services providers. Non-compliance with the GDPR may result in monetary penalties of up to €20 million or 4% of worldwide revenue, whichever is higher. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of personal data, such as healthcare data or other sensitive information, could greatly increase our cost of providing our products and services or even prevent us from offering certain services in jurisdictions that we may operate in.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products. For example, in March 2010, the ACA was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% (as of 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for manufacturers' outpatient drugs coverage under Medicare Part D; subjects drug manufacturers to new annual fees based on pharmaceutical companies' share of sales to federal healthcare programs; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in and conduct comparative clinical effectiveness research, along with funding for such research; and established the Center for Medicare Innovation at Centers for Medicare & Medicaid Services, or CMS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, various portions of the ACA are currently undergoing legal and constitutional challenges in the Fifth Circuit Court and the United States Supreme Court, and the Trump Administration has issued various Executive Orders that eliminated cost sharing subsidies and various provisions that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Additionally, Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended. We cannot predict what affect further changes to the ACA would have on our business.

In addition, the Budget Control Act of 2011 and the Bipartisan Budget Act of 2015 led to aggregate reductions of Medicare payments to providers of up to 2% per fiscal year that will remain in effect through 2027 unless additional Congressional action is taken. Further, on January 2, 2013, the American Taxpayer Relief Act was signed into law, which, among other things, reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for pharmaceutical products. Individual states in the United States have also become increasingly active in proposing and passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Finally, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA -approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

We expect that additional foreign, federal and state healthcare reform measures will be adopted in the future, any of which could limit the amounts that foreign federal and state governments will pay for healthcare products and services, which could result in limited coverage and reimbursement and reduced demand for our products, if approved, or additional pricing pressures.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any gene therapies for which we obtain regulatory approval. In the United States and markets in other countries, sales of any gene therapies for which we receive regulatory approval for commercial sale will depend, in part, on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. A decision by a third-party payor not to cover our gene therapies could reduce physician utilization of our products once approved and have a material adverse effect on our sales, results of operations and financial condition. Moreover, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

In addition, coverage and reimbursement for products can differ significantly from payor to payor. One third-party payor's decision to cover a particular medical product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate.

As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payor separately and will be a time-consuming process.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain and maintain coverage and reimbursement for any product, we may need to conduct expensive clinical trials in order to demonstrate the medical necessity and cost-effectiveness of such product, in addition to the costs required to obtain regulatory approvals. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit.

Outside of the United States, the pricing of pharmaceutical products is subject to governmental control in many countries. For example, in the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular therapy to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. Other countries may allow companies to fix their own prices for products, but monitor and control product volumes and issue guidance to physicians to limit prescriptions. Efforts to control prices and utilization of pharmaceutical products and medical devices will likely continue as countries attempt to manage healthcare expenditures.

Employees

As of December 31, 2019, we had 85 full-time employees, 28 of whom have Ph.D. or M.D. degrees. Of these full-time employees, 60 employees are engaged in research and development activities and 25 employees are engaged in finance, legal, human resources, facilities and general management. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relationship with our employees to be good.

Website Access to Reports

We are subject to the informational requirements of the Exchange Act and are required to file annual, quarterly and current reports, proxy statements and other information with the SEC. You can read our SEC filings at the SEC's website at www.sec.gov. We also maintain a website at www.avrobio.com. You may access, free of charge, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and any amendments to those reports, as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC.

Item 1A. Risk Factors

Investing in our common stock involves a high degree of risk. You should carefully consider the following risks and uncertainties, together with all other information in this Annual Report on Form 10-K, including our consolidated financial statements and related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," as well as our other filings with the Securities and Exchange Commission, or the SEC, before investing in our common stock. Any of the risk factors we describe below could adversely affect our business, financial condition or results of operations. The market price of our common stock could decline if one or more of these risks or uncertainties were to occur, which may cause you to lose all or part of the money you paid to buy our common stock. Additional risks that are currently unknown to us or that we currently believe to be immaterial may also impair our business. Certain statements below are forward-looking statements. See "Forward-Looking Information" in this Annual Report on Form 10-K.

Risks related to our business, financial position and need for additional capital

We have incurred net losses since inception. We expect to incur net losses for the foreseeable future and may never achieve or maintain profitability.

Since inception, we have incurred net losses. We incurred net losses of $73.0 million and $46.4 million for the years ended December 31, 2019 and 2018, respectively. We historically financed our operations primarily through private placements of our preferred stock and, more recently, our initial public offering and follow-on public offerings of our common stock. We have devoted substantially all of our efforts to research and development, including clinical and preclinical development of our product candidates, as well as assembling our team. We expect that it will be several years, if ever, before we have commercialized any product candidates. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if, and as, we:

- continue our development of our product candidates, including continuing enrollment in our ongoing Phase 2 clinical trial for AVR-RD-01, the investigator-sponsored Phase 1/2 clinical trial for AVR-RD-04 and our Phase 1/2 clinical trial for AVR-RD-02;
- initiate additional clinical trials and preclinical studies for our current and future product candidates;
- seek to identify and develop or in-license additional product candidates;
- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval;
- continue our implementation of our plato platform as we seek to industrialize our *ex vivo* lentiviral gene therapy approach into a robust, scalable and, if approved, commercially viable process;
- hire and retain additional personnel, such as clinical, quality control, commercial and scientific personnel;
- expand our office space, infrastructure and facilities to accommodate our growing employee base, including adding equipment and physical infrastructure to support our research and development; and
- continue to incur additional public company-related costs.

To become and remain profitable, we must develop and eventually commercialize product candidates with significant market potential. This will require us to be successful in a range of challenging activities, and our expenses will increase substantially as we seek to complete preclinical and clinical trials of our product candidates, and manufacture, market and sell these or any future product candidates for which we may obtain marketing approval, if any, and satisfy any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company also could cause you to lose all or part of your investment.

We have never generated revenue from product sales and do not expect to do so for the next several years, if ever.

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with collaborative partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, our product candidates. We do not anticipate generating revenues from product sales for the next several years, if ever. Our ability to generate future revenues from product sales depends heavily on our, or our collaborators', success in:

- completing research and preclinical and clinical development of our product candidates and identifying new lentiviral-based gene therapy product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical trials;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval by establishing a sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- qualifying for adequate coverage and reimbursement by government and third-party payors for our product candidates;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and the market demand for our product candidates, if approved;
- obtaining market acceptance of our product candidates, if approved, as a viable treatment option;
- addressing any competing technological and market developments;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements; and
- attracting, hiring and retaining qualified personnel.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA or other foreign regulatory authorities to perform clinical and other studies in addition to those that we currently anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

We will need additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

As of December 31, 2019, we had cash and cash equivalents of $187.0 million. We believe that our existing cash and cash equivalents as of December 31, 2019, together with the estimated net proceeds of $93.5 million from the follow-on offering of common stock we completed in February 2020, will enable us to fund our operating expenses and capital expenditure requirements into the second quarter of 2022. This forecast of cash resources is forward-looking information that involves risks and uncertainties, and the actual amount of our expenses could vary materially and adversely as a result of a number of factors. We have based our estimates on assumptions that may prove to be wrong, and our expenses could prove to be significantly higher than we currently anticipate.

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates and continue to enhance and optimize our vector technology and manufacturing processes. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant expenses related to product sales, medical affairs, marketing, manufacturing and distribution. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on reasonable terms, we would be forced to delay, reduce or eliminate certain of our research and development programs. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials for our other product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;

- the costs of future activities, including product sales, medical affairs, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers;
- revenue, if any, received from commercial sale of our products, should any of our product candidates receive marketing approval;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the terms of our current and any future license agreements and collaborations; and
- the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our product revenues, if any, will be derived from or based on sales of products that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or cause us to relinquish valuable rights.

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity, convertible debt securities or other equity-based derivative securities, your ownership interest will be diluted and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. Any additional indebtedness we incur would result in increased fixed payment obligations and could involve restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our common stock to decline and existing stockholders may not agree with our financing plans or the terms of such financings. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, or our product candidates, or grant licenses on terms unfavorable to us. Adequate additional financing may not be available to us on acceptable terms, or at all.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We are a clinical-stage company founded in November 2015. Our operations to date have been limited to corporate organization, recruiting key personnel, business planning, raising capital, acquiring rights to our technology, identifying potential product candidates, undertaking preclinical studies and planning and supporting clinical trials of our product candidates and establishing research and development and manufacturing capabilities. Although we initiated our ongoing Phase 2 clinical trial for AVR-RD-01 in June 2018, the first patient in the ongoing investigator-sponsored clinical trial of AVR-RD-04 was dosed in October 2019, and patient enrollment has commenced for our ongoing Phase 1/2 clinical trial of AVR-RD-02, we have not yet demonstrated the ability to complete clinical trials of our product candidates, obtain marketing approvals, manufacture products on a clinical or commercial scale or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history. In addition, as an early-stage company, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors.

Risks related to the discovery and development of our product candidates

Our lentiviral-based gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and of subsequently obtaining regulatory approval.

We have concentrated our research and development efforts on our lentiviral-based gene therapy approach, and our future success depends on our successful development of viable gene therapy product candidates. There can be no assurance that we will not experience problems or delays in developing new product candidates and that such problems or delays will not cause unanticipated costs, or that any such development problems can be solved. For example, the implementation of our plato platform and upgrades, including our transition to TDM conditioning using busulfan for our single-agent conditioning regimen, may result in delays or setbacks in our research and development activities, and we may not realize the intended benefits of these efforts. In addition, we may also experience delays in developing a sustainable, reproducible and scalable manufacturing process or transferring that process to commercial partners, which may prevent us from completing our clinical studies or commercializing our products on a timely or profitable basis, if at all. For example, as of March 6, 2020 we have only dosed one patient using our plato platform, which we plan to utilize for the majority of patients in our ongoing Phase 2 clinical trial for AVR-RD-01 and all patients in the Phase 1/2 clinical trial of AVR-RD-02. Our implementation of the LV2 lentiviral vector or of our cell processing to an industrialized, automated closed system using disposable supplies may not be successful or may experience unforeseen delays, which may cause shortages or delays in the supply of our products available for clinical trials and future commercial sales, if any, or impair our research and development efforts, including those in our ongoing and future clinical trials. In addition, there is no assurance that products using our proprietary LV2 lentiviral vector or manufactured using this automated system will ultimately achieve the same favorable preliminary results observed to date in the Phase 1 and Phase 2 clinical trials of AVR-RD-01.

In addition, the clinical trial requirements of the FDA and other foreign regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied product candidates. To date, only a limited number of gene therapies have received marketing authorization from the FDA or foreign regulatory authorities. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States, Canada or other major markets or how long it will take to commercialize our product candidates, if any are approved. Approvals by foreign regulatory authorities may not be indicative of what the FDA may require for approval, and vice versa.

Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. The FDA has established the Office of Tissues and Advanced Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise the CBER in its review. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the United States National Institutes of Health, or NIH, also are subject to the NIH Guidelines, under which supervision of human gene transfer trials includes evaluation and assessment by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. If we were to engage an NIH-funded institution to conduct a clinical trial, that institution’s IBC as well as its institutional review board, or IRB, would need to review the proposed clinical trial to assess the safety of the trial. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates. Similarly, foreign regulatory authorities may issue new guidelines concerning the development and marketing authorization for gene therapy medicinal products and require that we comply with these new guidelines.

The FDA, NIH and the European Medicines Agency, or EMA, have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as the U.S. congressional committees and other governments or governing agencies, have also expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates.

These regulatory review committees and advisory groups and any new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups, and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of certain of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects would be materially and adversely affected.

The FDA continues to develop its approach to assessing gene and cell therapy products. For example, the agency has released a series of draft guidance documents relating to, among other topics, various aspects of gene therapy product development, review, and approval, including aspects relating to clinical and manufacturing issues related to gene therapy products. We cannot be certain whether such guidance will be relevant to or have an impact on our gene therapy candidates or the duration or expense of any applicable regulatory development and review processes.

Our product candidates and the process for administering our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following any potential marketing approval.

During the conduct of clinical trials, patients may experience changes in their health, including illnesses, injuries, discomforts or a fatal outcome. It is possible that as we test AVR-RD-01, AVR-RD-04, AVR-RD-02 or other product candidates in larger, longer and more extensive clinical programs, or as use of our product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier clinical trials, as well as conditions that did not occur or went undetected in previous clinical trials, will be reported by patients. Gene therapies are also subject to the potential risk that occurrence of adverse events will be delayed following administration of the gene therapy due to persistent biological activity of the genetic material or other components of the vectors used to carry the genetic material. Many times, side effects are only detectable after investigational products are tested in larger scale, pivotal clinical trials or, in some cases, after they are made available to patients on a commercial scale after approval. If additional clinical experience indicates that any of our product candidates have side effects or causes serious or life-threatening side effects, the development of the product candidate may fail or be delayed, or, if the product candidate has received regulatory approval, such approval may be revoked or limited.

There have been several significant adverse side effects in gene therapy treatments in the past, including multiple reported cases of leukemia, myelodysplastic syndrome and death seen in other clinical trials. Gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. Possible adverse side effects that may occur with treatment with gene therapy products include an immunologic reaction early after administration that could substantially limit the effectiveness of the treatment or represent safety risks for patients. Another traditional safety concern for gene therapies using viral vectors has been the possibility of insertional mutagenesis by the vectors, leading to malignant transformation of transduced cells. While our lentiviral gene therapy approach is designed to avoid immunogenicity against the vector after administration, there can be no assurance that patients would not create antibodies that may impair treatment. If any of our gene therapy product candidates demonstrates adverse side effects at unacceptable rates or degrees of severity, we may decide or be required to halt or delay clinical development of such product candidates.

In addition to side effects caused by our product candidates, the conditioning, administration process or related procedures, which we evaluate from time to time as part of our process improvement and optimization efforts, also can cause adverse side effects. A gene therapy patient is generally administered one or more myeloablative drugs to remove stem cells from the bone marrow to create sufficient space in the bone marrow for the modified gene-corrected stem cells to engraft and produce their progeny. This procedure transiently compromises the patient’s immune system, known as neutropenia, and ability to form blood clots, known as thrombocytopenia.

In 2019 we began transitioning, in connection with our company-sponsored clinical trials, towards a new conditioning regimen for our product candidates utilizing busulfan as the myeloablative conditioning agent instead of the melphalan that we previously used. The use of this conditioning regimen is designed to utilize therapeutic drug monitoring, or TDM, to achieve a balance between the removal of a sufficient amount of bone marrow cells from a patient against potential risks such as toxicity or graft failure. While we anticipate that the conditioning regimen may be performed during a limited hospital stay or potentially through an outpatient procedure, on a case-by-case basis as directed by a patient’s physician, we cannot guarantee that the conditioning will not require a lengthier hospitalization. Our conditioning regimens may not be successful or may nevertheless result in adverse side effects. For example, in the ongoing investigator-sponsored Phase 1 clinical trial and our ongoing company-sponsored Phase 2 clinical trial of AVR-RD-01, as well as the investigator-sponsored Phase 1/2 clinical trial of AVR-RD-04, several adverse events, including suppression of neutrophils and platelet counts following the conditioning process, were observed. While such adverse events in connection with conditioning is expected, if in the future any such adverse events caused by the conditioning process or related procedures continue at unacceptable rates or degrees of severity, the FDA or other foreign regulatory authorities could order us to cease development of, or deny approval of, AVR-RD-01 or our other product candidates for any or all targeted indications. In addition, although in the future we may implement new procedures to screen for certain pre-cancerous genetic mutations prior to commencement of the conditioning regimen as an additional risk reduction measure, there can be no guarantees that these procedures, if implemented, would be successful. Even if we are able to demonstrate that adverse events are not product-related, such occurrences could adversely affect patient recruitment or the ability of enrolled patients to complete the clinical trial.

Additionally, if any of our product candidates receives marketing approval, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, to ensure that the benefits outweigh its risks, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients, a communication plan to health care practitioners, and restrictions on how or where the product can be distributed, dispensed or used. Furthermore, if we or others later identify undesirable side effects caused by AVR-RD-01, AVR-RD-04, AVR-RD-02 or our other product candidates, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product candidate;
- regulatory authorities may require additional warnings on the label;
- we may be required to change the way a product candidate is distributed, dispensed, or administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and could significantly harm our business, prospects, financial condition and results of operations.

We have never completed a pivotal clinical trial, and may be unable to do so for any product candidates we may develop, including AVR-RD-01, AVR-RD-04 and AVR-RD-02.

We are at an early stage of development for all of our product candidates including AVR-RD-01, AVR-RD-04 and AVR-RD-02. As of March 6, 2020, our product candidate AVR-RD-01 has been administered to only five patients in an ongoing investigator-sponsored Phase 1 clinical trial and to four patients in our ongoing Phase 2 clinical trial, and AVR-RD-04 has been administered to only one patient in the ongoing investigator-sponsored Phase 1/2 clinical. Although patient enrollment has commenced for our Phase 1/2 clinical trial of AVR-RD-02, we do not expect to dose the first patient until the second quarter of 2020. These ongoing clinical trials must be completed, as well as potentially additional pivotal clinical trials in order to obtain FDA approval to market these product candidates. We have limited experience in preparing, submitting and prosecuting regulatory filings, and have not previously submitted a biologics license application, or BLA, for any product candidate.

Carrying out later-stage clinical trials is a complicated and lengthy process, and we do not expect that all data from patients participating in the clinical trials will be relevant or meaningful. For example, the primary efficacy endpoint of our Phase 2 clinical trial of AVR-RD-01 is the change, from baseline to one year post-treatment with AVR-RD-01, in the average number of Gb3 inclusions per PTC, as measured in a patient kidney biopsy. The second patient in the Phase 2 trial has an N215S genotype, which is associated with a late-onset cardiac variant phenotype and lower plasma lyso-Gb3 levels. This patient’s cardiac variant phenotype does not typically result in Gb3 accumulation in the kidney and skin, and accordingly we do not expect that data obtained from this patient will have a meaningful impact on certain efficacy endpoints in our Phase 2 clinical trial, including kidney and skin biopsies. Nonetheless, there may be other important insights derived from data collected from this patient in the Phase 2 clinical trial.

In addition, we have not yet conducted any company-sponsored clinical trials of any of our product candidates in the United States, and our interactions with the FDA have generally been limited. We cannot be certain how many additional clinical trials of AVR-RD-01, AVR-RD-04, AVR-RD-02 or any other product candidates will be required or how such trials should be designed. In order to commence a clinical trial in the United States, we are required to seek FDA acceptance of an IND for each of our product candidates. We cannot be sure any IND we submit to the FDA, or any similar clinical trial application we submit in other countries, will be accepted. While we have received clearance from the FDA to commence clinical testing in the United States for AVR-RD-01 and AVR-RD-02, and the sponsor of the investigator-led clinical trial for AVR-RD-04 has received the same, there can be no assurance that we will be able to submit and secure similar clearances for any of our other product candidates. We may also be required to conduct additional preclinical testing prior to filing an IND for any of our product candidates, and the results of any such testing may not be positive. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to a BLA submission and approval of AVR-RD-01, AVR-RD-04, AVR-RD-02 or any of our other product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing AVR-RD-01, AVR-RD-04, AVR-RD-02 or any of our other product candidates.

The ongoing Phase 1 clinical trial of AVR-RD-01 is an investigator-sponsored trial being conducted by University Health Network. In addition, the ongoing Phase 1/2 clinical trial of AVR-RD-04 is also an investigator-sponsored clinical trial, which is being conducted by our collaborators at the University of California, San Diego. We do not control the design or administration of investigator-sponsored trials, nor the submission or approval of any IND or foreign equivalent required to conduct these trials, and the investigator-sponsored trials could, depending on the actions of such third parties, jeopardize the validity of the clinical data generated, identify significant concerns with respect to our product candidates that could impact our findings or clinical trials, and adversely affect our ability to obtain marketing approval from the FDA or other applicable regulatory authorities. To the extent the results of this or other investigator-sponsored trials are inconsistent with, or different from, the results of our planned company-sponsored trials or raise concerns regarding our product candidates, the FDA or a foreign regulatory authority may question the results of the company-sponsored trial, or subject such results to greater scrutiny than it otherwise would. In these circumstances, the FDA or such foreign regulatory authorities may require us to obtain and submit additional clinical data, which could delay clinical development or marketing approval of our product candidates. In addition, while investigator-sponsored trials could be useful to inform our own clinical development efforts, there is no guarantee that we will be able to use the data from these trials to form the basis for regulatory approval of our product candidates.

Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.

Results from preclinical studies or early clinical trials are not necessarily predictive of future clinical trial results and are not necessarily indicative of final results. For example, there can be no assurance that prior results, such as signals of safety, activity or durability of effect, observed from preclinical studies or clinical trials will be replicated or will continue in ongoing or future studies or trials. Furthermore, preliminary results may not be indicative of the final results of a trial after all data have been collected and analyzed. Based on results observed from ongoing trials of AVR-RD-01, there can be no assurance that increased levels of AGA in patients treated with AVR-RD-01 will be maintained over time. In addition, while the first, third and fifth patients from the ongoing investigator-sponsored Phase 1 clinical trial of AVR-RD-01 discontinued ERT, there can be no assurance that these patients, or others who in the future may discontinue ERT, will remain off ERT. The initial results from the investigator-sponsored clinical trial of AVR-RD-04 only represent three months of clinical data from one patient, and there is no assurance that future clinical data from this patient or other patients will produce similar results. There is a high failure rate for gene therapy and biologic product candidates proceeding through clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, the design of a pivotal clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. Our company has limited experience in designing and conducting clinical trials and we may be unable to design and execute a clinical trial to support regulatory approval. To date, we have not received definitive guidance from the FDA or other foreign regulatory bodies regarding the necessary endpoints for approval of any of our product candidates, including AVR-RD-01, AVR-RD-04 and AVR-RD-02. While we are aware that the FDA utilized an efficacy endpoint based on patients' kidney biopsy in the recent approval of Migalastat for Fabry disease, for which we are also measuring as our primary efficacy endpoint in our ongoing Phase 2 clinical trial of AVR-RD-01, there can be no guarantees that regulatory agencies will permit us to use the same endpoint in connection with further development of AVR-RD-01. Therefore, there are no assurances that the FDA or other foreign regulatory bodies will find the efficacy endpoints we propose in future pivotal trials to be sufficiently validated and clinically meaningful, or that our product candidates will achieve the pre-specified endpoints in future pivotal trials to a degree of statistical significance. We also may experience regulatory delays or rejections as a result of many factors, including due to changes in regulatory policy during the period of our product candidate development. Although patient enrollment has commenced for our Phase 1/2 clinical trial of AVR-RD-02, we have not dosed any patients, and our AVR-RD-03 product candidate is in preclinical development and has not yet been tested in humans. Any of our other current or future product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies. Any such failure would cause us to abandon the product candidate.

Additionally, the clinical trials performed to date have been open-label studies and have been conducted at a limited number of clinical sites on a limited number of patients. An "open-label" clinical trial is one where both the patient and investigator know whether the patient is receiving the investigational product candidate or either an existing approved drug or placebo. Most typically, open-label clinical trials test only the investigational product candidate and sometimes may do so at different dose levels. Open-label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in open-label clinical trials are aware when they are receiving treatment. Open-label clinical trials may be subject to a "patient bias" where patients perceive their symptoms to have improved merely due to their awareness of receiving an experimental treatment. Moreover, patients selected for early clinical studies often include the most severe sufferers and their symptoms may have been bound to improve notwithstanding the new treatment. In addition, open-label clinical trials may be subject to an "investigator bias" where those assessing and reviewing the physiological outcomes of the clinical trials are aware that patients have received treatment and may interpret the information more favorably given this knowledge.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on our ability to recruit patients to participate as well as the completion of required follow-up periods. Patients may be unwilling to participate in our gene therapy clinical trials because of negative publicity from adverse events related to the biotechnology or gene therapy fields, competitive clinical trials for similar patient populations, clinical trials in product candidates employing our vectors, the existence of current treatments or for other reasons. In addition, the indications that we are currently targeting and may in the future target are rare diseases, which may limit the pool of patients that may be enrolled in our ongoing or planned clinical trials. The timeline for recruiting patients, conducting studies and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics, to complete our clinical trials in a timely manner. For example, in 2017, the ongoing investigator-sponsored Phase 1 clinical trial of AVR-RD-01 encountered delays in the enrollment of patients due to delays in identifying patients for enrollment and the evaluation of information from screened potential trial participants. In 2019, we encountered delays in the enrollment of patients in the company-sponsored Phase 1/2 clinical trial of AVR-RD-02 for Gaucher disease. While a number of patients had been identified for the Phase 1/2 clinical trial, we encountered patient pre-screening failures that impacted the commencement of enrollment.

Patient enrollment and trial completion is affected by factors including the:

- size of the patient population and process for identifying patients;
- design of the trial protocol;
- eligibility and exclusion criteria;
- perceived risks and benefits of the product candidate under study;
- perceived risks and benefits of gene therapy-based approaches to treatment of diseases, including any required pretreatment conditioning regimens;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;
- availability of genetic testing for potential patients;
- proximity and availability of clinical trial sites for prospective patients;
- ability to obtain and maintain subject consent;
- risk that enrolled patients will drop out before completion of the trial;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

We anticipate expanding our patient enrollment activities to include patients who reside in a country other than the country where the applicable clinical site is located, and who would be required to travel for some or all of the clinical testing and procedures required for patients in the applicable clinical trial. We may encounter logistical and regulatory challenges that could delay or prevent any such international patients from successfully enrolling and completing clinical trial procedures, including delays in processing or obtaining patient travel visas or denials of entry at borders, potential travel disruptions, or de-prioritization or unavailability of resources at clinical sites for non-resident international clinical trial participants, any of which could delay our progress and completion of planned clinical trials and which would have an adverse effect on our business.

Our current product candidates are being developed to treat rare conditions. We plan to seek initial marketing approvals in the United States, Europe and certain other major markets, including Japan. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by FDA or other foreign regulatory authorities. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;
- the absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, financial condition, results of operations and prospects.

Business interruptions resulting from the coronavirus disease (COVID-19) outbreak or similar public health crises could cause a disruption of the development of our product candidates and adversely impact our business.

Public health crises such as pandemics or similar outbreaks could adversely impact our business. In December 2019, a novel strain of a virus named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), or coronavirus, which causes coronavirus disease, or COVID-19, was reported to have surfaced in Wuhan, China and has reached multiple other regions and countries, including Cambridge, Massachusetts where our primary office and laboratory space is located. The coronavirus pandemic is evolving, and to date has led to the implementation of various responses, including government-imposed quarantines, travel restrictions and other public health safety measures. The extent to which the coronavirus impacts our operations or those of our third party partners will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration of the outbreak, new information that may emerge concerning the severity of the coronavirus and the actions to contain the coronavirus or treat its impact, among others.

Additionally, timely enrollment in our clinical trials is dependent upon global clinical trial sites which may be adversely affected by global health matters, such as pandemics. We are currently conducting clinical trials for our product candidates in the United States, Canada and Australia, and plan to expand to other geographies including Japan, Europe and Israel, and many of these regions are currently being affected by the coronavirus. Some factors from the coronavirus outbreak that may delay or otherwise adversely affect enrollment in the clinical trials of our product candidates, as well as our business generally, include:

- the potential diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, including the attention of physicians serving as our clinical trial investigators, hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- limitations on travel that could interrupt key trial activities, such as clinical trial site initiations and monitoring, domestic and international travel by employees, contractors or patients to clinical trial sites, including any government-imposed travel restrictions or quarantines that may impact the ability or willingness of patients, employees or contractors to travel to our clinical trial sites or secure visas or entry permissions, any of which could delay or adversely impact the conduct or progress of our clinical trials;
- interruption in global shipping affecting the transport of clinical trial materials, such as patient samples, investigational drug product and conditioning drugs and other supplies used in our clinical trials; and
- business disruptions caused by potential workplace, laboratory and office closures and an increased reliance on employees working from home, disruptions to or delays in ongoing laboratory experiments and operations, staffing shortages, travel limitations or mass transit disruptions, any of which could adversely impact our business operations or delay necessary interactions with local regulators, ethics committees and other important agencies and contractors.

These and other factors arising from the coronavirus could worsen in countries that are already afflicted with the coronavirus or could continue to spread to additional countries, each of which could further adversely impact our ability to conduct clinical trials and our business generally, and could have a material adverse impact on our operations and financial condition and results.

We may encounter substantial delays in our clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical study sites;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical study site;
- delays in recruiting suitable patients to participate in our clinical studies;
- imposition of a clinical hold by regulatory agencies, after an inspection of our clinical study operations or study sites;
- failure by our CROs, other third parties or us to adhere to clinical study requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical study sites or patients dropping out of a study;
- the occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues. In addition, if we make changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions, which could delay our clinical development plan or marketing approval for our product candidates. For example, for our Phase 2 clinical trial of AVR-RD-01, we have transitioned our lentiviral vectors to an LV2 version in connection with our plato platform implementation. In addition, the transition from LV1 to LV2 has required (and is anticipated to continue to require) submission of relevant data to the applicable regulatory authorities in connection with certain of our regulatory filings, including our INDs and clinical trial applications, to demonstrate analytic comparability between LV1 and LV2. Our IND application for our planned Phase 2 clinical study of AVR-RD-01 for Fabry disease in the United States, which was cleared by the FDA in April 2019, included data to demonstrate comparability between LV1 and LV2 and a transition to an automated manufacturing platform. In addition, our CTA (including amendments) and IND for our Phase 1/2 clinical study of AVR-RD-02 for Gaucher disease in Canada and the United States, for which Health Canada has issued no objection letters and the FDA has cleared, respectively, included data utilizing LV2 and our automated manufacturing platform. While these applications included data relating to our LV2 lentiviral vector and our automated manufacturing process, which are elements of our plato platform, and allow us to commence clinical trials incorporating such elements, there can be no assurance that the FDA, Health Canada or other regulatory authorities will not require us to undertake additional actions in connection with our transition to our plato platform, including submission of additional comparability studies in connection with future regulatory filings, which may result in delays, suspension or termination of ongoing or future clinical trials, or our inability to conduct our trials according to the plans or the timelines that we have envisioned. For example, the Phase 1/2 investigator-sponsored clinical study of AVR-RD-04 for cystinosis in the United States, which has been cleared by the FDA, does not include our LV2 lentiviral vector or our automated manufacturing platform, and we anticipate that we will be required to submit comparability data in future regulatory filings relating to our transition to LV2 and the automated manufacturing platform. Any such filings may result in delay, suspension or termination of ongoing or future clinical trials pending our submission, and the applicable regulatory agency's review, of such updates. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates, if approved, or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

If the results of our clinical studies are inconclusive or if there are safety concerns or adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling or a REMS that includes significant use or distribution restrictions or safety warnings;
- be subject to changes with the way the product is administered;
- be required to perform additional clinical studies to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its distribution in the form of a REMS;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and impair our ability to commercialize our products.

Even if we complete the necessary preclinical and clinical studies, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate and the approval may be for a narrower indication than we seek.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical studies, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical studies and the review process. Regulatory agencies also may approve a treatment candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. If we are unable to obtain necessary regulatory approvals, our business, prospects, financial condition and results of operations may suffer.

Certain of our clinical trials, including the ongoing investigator-sponsored clinical trial of AVR-RD-01, a portion of our company-sponsored clinical trial of AVR-RD-01, and the investigator-sponsored clinical trial of AVR-RD-04, do not utilize our commercial-scale plato platform. While we have submitted and intend to continue to submit comparability studies to the FDA and other regulatory agencies, as needed, with respect to our implementation of our commercial-scale plato platform, there can be no assurance that the FDA or other regulatory agencies will not in the future require us to conduct additional preclinical studies or clinical trials with respect to these programs or our other product candidates that could result in delays in our development or commercialization programs of our product candidates, if approved, and additional expenses and otherwise could adversely affect our business.

We intend to continue implementing our commercial-scale plato platform, including heightened vector efficiency, our closed, automated manufacturing system and utilization of a TDM conditioning regimen with busulfan, in connection with each of our investigational product candidates. We have developed the plato platform to form the backbone of our commercial programs, with the intent of replacing our original academic platform with improved solutions for delivering our gene therapy candidates to patients in multiple disease indications. We believe improvements from our plato platform may lead to better patient outcomes with our gene therapy candidates. In order to implement this transition, we have been and will be required to conduct additional studies to bridge our modified product candidates to earlier versions, which could delay our clinical development plans or marketing approvals, if any, including for AVR-RD-01, where the ongoing investigator-sponsored clinical trial does not use the plato platform, a portion of our Company-sponsored clinical trial for AVR-RD-01, and for AVR-RD-04 where the investigator-sponsored clinical trial will not utilize the plato platform. For example, we have transitioned our AVR-RD-01 lentiviral vectors to an LV2 version, and the fourth patient in our Phase 2 trial of AVR-RD-01 was dosed in 2019 using the plato platform. While LV2 is intended to confer improvements in transduction efficiency in viral production, there is no guarantee that we can realize these intended benefits. In addition, the transition from LV1 to LV2 has required (and is anticipated to continue to require) submission of relevant data to the applicable regulatory authorities in connection with certain of our regulatory filings, including our INDs and clinical trial applications, to demonstrate analytic comparability between LV1 and LV2. Our IND application for our planned Phase 2 clinical study of AVR-RD-01 for Fabry disease in the United States, which was cleared by the FDA in April 2019, included data to demonstrate comparability between LV1 and LV2 and a transition to an automated manufacturing platform, which are elements of our plato platform. In addition, our CTA (including amendments) and IND for our Phase 1/2 clinical study of AVR-RD-02 for Gaucher disease in Canada and the United States, for which Health Canada has issued no objection letters and the FDA has cleared, respectively, included data utilizing LV2 and our automated manufacturing platform. Nevertheless, there can be no assurance that the FDA, Health Canada or other regulatory agencies will not in the future require us to conduct additional preclinical studies or clinical trials with respect to these programs or our other product candidates, which may result in delay, suspension or termination of ongoing or future clinical trials. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates, if approved, or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

While we intend to seek designations for our product candidates with the FDA and comparable foreign regulatory authorities that are intended to confer benefits such as a faster development process or an accelerated regulatory pathway, there can be no assurance that we will successfully obtain such designations. In addition, even if one or more of our product candidates are granted such designations, we may not be able to realize the intended benefits of such designations.

The FDA and comparable foreign regulatory authorities offer certain designations for product candidates that are designed to encourage the research and development of product candidates that are intended to address conditions with significant unmet medical need. These designations may confer benefits such as additional interaction with regulatory authorities, a potentially accelerated regulatory pathway and priority review. However, there can be no assurance that we will successfully obtain such designations for any of our product candidates. In addition, while such designations could expedite the development or approval process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

For example, we may seek a Breakthrough Therapy Designation for some of our product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA are also eligible for accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

In addition, we may seek Fast Track Designation for some of our product candidates. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, there can be no assurance that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a Fast Track Designation does not provide assurance of ultimate FDA approval. In addition, the FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

In addition, we may seek a regenerative medicine advanced therapy, or RMAT, designation for some of our product candidates. An RMAT is defined as cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Gene therapies, including genetically modified cells that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy. The RMAT program is intended to facilitate efficient development and expedite review of RMATs, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition. A new drug application or a BLA for an RMAT may be eligible for priority review or accelerated approval through (1) surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit or (2) reliance upon data obtained from a meaningful number of sites. Benefits of such designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. RMAT designation is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a regenerative medicine advanced therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of RMAT designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify for RMAT designation, the FDA may later decide that the biological products no longer meet the conditions for qualification.

Outside of the United States, we intend to develop AVR-RD-01 in Japan under the purview of the Japanese Pharmaceutical and Medical Device Agency, or PMDA. Pursuant to Japan’s regenerative medicine law, an expedited path to conditional approval may exist for regenerative medicine products that show sufficient safety evidence and signals of efficacy in a Phase 2 clinical trial. However, there can be no assurance that the results of our ongoing Phase 2 clinical trial will demonstrate the safety evidence and efficacy signals required for such conditional approval. In addition, this conditional approval is time-limited, and there must be an agreement as to follow-up collection of information to confirm efficacy and safety, similar to a post-marketing commitment in the United States.

We may be unable to obtain orphan drug designation for our product candidates and, even if we obtain such designation, we may not be able to realize the benefits of such designation, including potential marketing exclusivity of our product candidates, if approved.

Regulatory authorities in some jurisdictions, including the United States and other major markets, may designate drugs intended to treat conditions or diseases affecting relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, EMA’s Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product.

In December 2018, October 2019 and March 2020, the FDA granted our requests for orphan drug designation for AVR-RD-01 for the treatment of Fabry disease, AVR-RD-02 for the treatment of Gaucher disease and AVR-RD-04 for the treatment of cystinosis, respectively. To date, we have not requested orphan drug designation (or the foreign equivalent) for any other product candidates, and even if we do in the future there can be no assurances that the FDA or foreign regulatory authorities will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not mean that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or foreign regulatory authorities from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and 10 years in the European Union. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition in the United States. Even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

- the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or
- the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory oversight.

Even if we obtain any regulatory approval for our product candidates, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates also may be subject to a REMS, limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. For example, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. FDA guidance advises that patients treated with some types of gene therapy undergo follow-up observations for potential adverse events for as long as 15 years. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practices, or CGMP, requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory authority may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;

- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of products; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and adversely affect our business, financial condition, results of operations and prospects.

In addition, the FDA's policies, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

We face significant competition in our industry and there can be no assurance that our product candidates, if approved, will achieve acceptance in the market over existing established therapies. In addition, our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialize any of our product candidates.

We operate in a highly competitive segment of the biopharmaceutical market. We face competition from many different sources, including larger pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies and private and public research institutions. Our product candidates, if successfully developed and approved, will compete with established therapies, some of which are being marketed by large and international companies. In addition, we expect to compete with new treatments that are under development or may be advanced into the clinic by our competitors. There are a variety of product candidates, including gene therapies, in development for the indications that we are targeting.

We anticipate competing with the largest pharmaceutical companies in the world. For example, Sanofi Genzyme and Shire, acquired by Takeda Pharmaceutical Company Ltd., market the enzyme replacement therapies, or ERTs, that represent the standard of care for Fabry patients. Amicus has secured regulatory approval in the United States and Europe for Migalastat, its oral therapy for Fabry disease. For Gaucher disease, we expect to compete with existing enzyme replacement therapies marketed by Sanofi Genzyme, Shire, Protalix and Pfizer, as well as oral therapies marketed by Actelion and Sanofi. Sanofi also markets an enzyme replacement therapy for Pompe disease. Cystinosis is currently treated by therapies marketed by Horizon Orphan, Mylan, Chiesi, Recordati and Sigma Tau Pharmaceuticals, and Eloxx Pharmaceuticals has been advancing a new treatment in clinical trials, though in March 2020 it announced that its Phase 2 study of the new treatment has been discontinued. In addition, we may compete with other gene therapy companies in our industry such as bluebird bio and Spark Therapeutics (which was acquired by Roche in the fourth quarter of 2019). In particular, a number of gene therapy companies have announced preclinical or clinical adeno-associated virus, or AAV, based gene therapy programs that, if such programs are successful in obtaining regulatory approval, could compete with our gene therapies. These include companies such as Abeona, Amicus, Freeline, JCR Pharmaceuticals, Sangamo and uniQure which have announced gene therapy programs for Fabry disease; Freeline and Prevail which have announced gene therapy programs for Gaucher disease; and Abeona, Actus, Amicus, Audentes, Sarepta and Spark Therapeutics which have announced gene therapy programs for Pompe disease.

Many of our competitors have significantly greater financial, product candidate development, manufacturing and marketing resources than we do. Large pharmaceutical and biotechnology companies have extensive experience in clinical testing and obtaining regulatory approval for their products, and mergers and acquisitions within these industries may result in even more resources being concentrated among a smaller number of larger competitors. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel therapeutics or to in-license novel therapeutics that could make the product candidates that we develop obsolete. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our business would be materially and adversely affected if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, have broader market acceptance, are more convenient or are less expensive than any product candidate that we may develop.

Even if we obtain regulatory approval of our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances.

Our focus on developing our current product candidates may not yield any commercially viable products, and our failure to successfully identify and develop additional product candidates could impair our ability to grow.

As part of our growth strategy, we intend to identify, develop and market additional product candidates beyond our existing product candidates for Fabry disease, Gaucher disease, cystinosis and Pompe disease. We may spend several years completing our development of any particular current or future product candidates, and failure can occur at any stage. The product candidates to which we allocate our resources may not end up being successful. Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential than our product candidates. Our spending on current and future research and development programs may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate.

Because our internal research capabilities are limited, we may be dependent upon biotechnology companies, academic scientists and other researchers to sell or license product candidates, approved products or the underlying technology to us. The success of this strategy depends partly upon our ability to identify, select, discover and acquire promising product candidates and products.

In addition, certain of our current or future product candidates may not demonstrate in patients any or all of the pharmacological benefits we believe they may possess or compare favorably to existing, approved therapies, such as ERT. We have not yet succeeded and may never succeed in demonstrating efficacy and safety of our product candidates or any future product candidates in clinical trials or in obtaining marketing approval thereafter. Accordingly, our focus on treating these diseases may not result in the development of commercially viable products.

If we are unsuccessful in our development efforts, we may not be able to advance the development of our product candidates, commercialize products, raise capital, expand our business or continue our operations.

Risks related to our reliance on third parties

We expect to rely on third parties to conduct some or all aspects of our vector production, product manufacturing, protocol development, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.

We do not expect to independently conduct all aspects of our vector production, product manufacturing, protocol development, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to these items. For example, we have moved our cell processing to an automated, closed system with a single third-party supplier.

Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it could delay our product development activities. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. For example, for product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our preclinical and clinical studies are conducted in accordance with the study plan, protocols and regulatory requirements.

If our contract counterparties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the preclinical and clinical studies required to support approval of our product candidates or the FDA or other regulatory agencies may refuse to accept our clinical or preclinical data. For example, in 2017, the ongoing investigator-sponsored Phase 1 clinical trial of AVR-RD-01 encountered delays in the enrollment of patients due to delays in identifying patients for enrollment and the evaluation of information from screened potential trial participants. In 2019, we encountered delays in the enrollment of patients in the company-sponsored Phase 1/2 clinical trial of AVR-RD-02 for Gaucher disease. While a number of interested patients had been identified for the Phase 1/2 clinical trial, we encountered patient pre-screening failures that impacted the commencement of enrollment in these studies.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

Any of these events could lead to delays of our preclinical and clinical studies or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.

We currently have relationships with a limited number of suppliers for the manufacturing of our viral vectors and product candidates. Each supplier may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities.

All entities involved in the preparation of therapeutics for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical studies must be manufactured in accordance with CGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA's good laboratory practices, or GLP, and CGMP regulations enforced by the FDA through its facilities inspection program. Some of our contract manufacturers have not produced a commercially-approved product and have never been inspected by the FDA before. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit our manufacturing facilities or those of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

These factors could cause the delay of clinical studies, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our preclinical and clinical studies may be delayed.

We are dependent on a limited number of suppliers for some of our components and materials used in our product candidates.

We currently depend on a limited number of suppliers for some of the components necessary for our product candidates. We cannot be sure that these suppliers will remain in business, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to produce these materials for our intended purpose. Our use of a limited number of suppliers of raw materials, components and finished goods exposes us to several risks, including disruptions in supply, price increases, late deliveries and an inability to meet customer demand. There are, in general, relatively few alternative sources of supply for these components. These vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. Any disruption in supply from any supplier or manufacturing location could lead to supply delays or interruptions which would damage our business, financial condition, results of operations and prospects.

If we are required to switch to a replacement supplier, the manufacture and delivery of our product candidates could be interrupted for an extended period, adversely affecting our business. Establishing additional or replacement suppliers may not be accomplished quickly. If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. For example, the FDA could require additional supplemental data and clinical trial data if we rely upon a new supplier. While we seek to maintain adequate inventory of the components and materials used in our product candidates, any interruption or delay in the supply of components or materials, or our inability to obtain components or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to conduct our clinical trials and, if our product candidates are approved, to meet the demand of our customers and cause them to cancel orders.

In addition, as part of the FDA's approval of our product candidates, the FDA must review and approve the individual components of our production process, which includes the manufacturing processes and facilities of our suppliers. Our current suppliers have not undergone this process, nor have they had any components included in any product approved by the FDA.

Our reliance on these suppliers subjects us to a number of risks that could harm our reputation, business, and financial condition, including, among other things:

- the interruption of supply resulting from modifications to or discontinuation of a supplier's operations;
- delays in product shipments resulting from uncorrected defects, reliability issues, or a supplier's variation in a component;
- a lack of long-term supply arrangements for key components with our suppliers;
- the inability to obtain adequate supply in a timely manner, or to obtain adequate supply on commercially reasonable terms;
- difficulty and cost associated with locating and qualifying alternative suppliers for our components in a timely manner;
- production delays related to the evaluation and testing of products from alternative suppliers, and corresponding regulatory qualifications;
- a delay in delivery due to our suppliers prioritizing other customer orders over ours;
- damage to our reputation caused by defective components produced by our suppliers;
- increased cost of our warranty program due to product repair or replacement based upon defects in components produced by our suppliers; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

If any of these risks materialize, costs could significantly increase and our ability to conduct our clinical trials and, if our product candidates are approved, to meet demand for our products could be impacted.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to manufacture our vectors and our product candidates, and because we collaborate with various organizations and academic institutions on the advancement of our gene therapy approach, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets.

Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks related to commercialization of our product candidates

If we are unable to establish sales, distribution and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we will be unable to generate any product revenue.

We are in the preliminary stages of building our commercial organization. To successfully commercialize any of our current or future product candidates, if approved, we will need to develop these capabilities, either on our own or with others. The establishment and development of our own commercial team or the establishment of a contract sales force to market any product candidate we may develop will be expensive and time-consuming and could delay any product launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We may enter into collaborations regarding any approved product candidates with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any future collaborators do not commit sufficient resources to commercialize our product candidates, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded sales, distribution and marketing operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates, if approved. Without an internal team or the support of a third-party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

If the market opportunities for our product candidates are smaller than we believe they are, our product revenues may be adversely affected and our business may suffer.

We focus our research and product development on treatments for serious lysosomal diseases. Our understanding of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

Even if we obtain any regulatory approval for our product candidates, the commercial success of our product candidates will depend in part on the medical community, patients, and third-party payors accepting gene therapy products in general, and our product candidates in particular, as effective, safe and cost-effective. Any product that we bring to the market may not gain market acceptance by physicians, patients, third-party payors and others in the medical community. The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments, including any similar generic treatments;
- the efficacy and safety as demonstrated in pivotal clinical trials and published in peer-reviewed journals;
- the prevalence and severity of any adverse events or side effects, including any limitations or warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects resulting from the conditioning regimen for the administration of our product candidates;
- the ability to offer the products for sale at competitive prices;
- the clinical indications for which the products are approved by the FDA or comparable regulatory agencies;
- the relative convenience and ease of dosing and administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- restrictions on how the product is distributed;
- publicity concerning our products or competing products and treatments; and
- favorable third-party insurance coverage and sufficient reimbursement.

Sales of medical products also depend on the willingness of physicians to prescribe the treatment, which is likely to be based on a determination by these physicians that the products are safe, therapeutically effective and cost effective. In addition, the inclusion or exclusion of products from treatment guidelines established by various physician groups and the viewpoints of influential physicians can affect the willingness of other physicians to prescribe the treatment. We cannot predict whether physicians, physicians' organizations, hospitals, other healthcare providers, government agencies or private insurers will determine that our product is safe, therapeutically effective and cost effective as compared with competing treatments.

Even if a product candidate displays a favorable efficacy and safety profile in preclinical and clinical studies, market acceptance of the product, if approved for commercial sale, will not be known until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable.

If we obtain approval to commercialize our product candidates outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

We are currently conducting clinical trials for our product candidates in the United States, Canada and Australia, and plan to expand to other geographies including Japan, Europe and Israel. If any of our product candidates are approved for commercialization, we may enter into agreements with third parties to market them on a worldwide basis or in more limited geographical regions. We expect that we will be subject to additional risks related to entering into international business relationships, including:

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;

- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

The insurance coverage and reimbursement status of newly-approved products are uncertain. Failure to obtain or maintain adequate coverage and reimbursement for any of our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. In the United States, recently enacted legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our or their commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenue we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if any product candidates we may develop obtain marketing approval.

Our ability to successfully commercialize our product candidates or any other products that we or they may develop also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers, and other organizations. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford treatments. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize our product candidates, if approved. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Adequate coverage and reimbursement from governmental healthcare programs and commercial payors are critical to new product acceptance. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which drugs and treatments they will cover and the amount of reimbursement. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor’s determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe and certain other major markets where we plan to commercialize may put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems, and pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates to other available therapies. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medicines, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

Moreover, efforts by governmental and third-party payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Due to the novel nature of our technology and the potential for our product candidates to offer therapeutic benefit in a single administration, we face uncertainty related to pricing and reimbursement for these product candidates.

Our target patient populations are relatively small, as a result of which the pricing and reimbursement of our product candidates, if approved, must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to our product candidates (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our product candidates, if approved.

Gene therapies are novel, complex and difficult to manufacture. We could experience production problems that result in delays in our development or commercialization programs or otherwise adversely affect our business.

The manufacturing process we use to produce our product candidates is complex, novel and has not been validated for commercial use. Several factors could cause production interruptions, including equipment malfunctions, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of our suppliers.

Our product candidates require processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of a biologic such as ours generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product will perform in the intended manner. Accordingly, we and our manufacturing suppliers employ multiple steps to control the manufacturing process with the goal of ensuring that the product candidate is made strictly and consistently in compliance with the process. Problems with the manufacturing process, including even minor deviations from the intended process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA or other applicable regulatory standards or specifications with consistent and acceptable production yields and costs.

In addition, the FDA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA or other foreign regulatory authorities may require that we not distribute a lot until the agency authorizes its release. Even slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures or product recalls. There is no assurance we will not experience lot failures in the future. Lot failures or product recalls could cause us to delay clinical trials, or, if approved, commercial product launches, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects.

Healthcare legislative reform measures and constraints on national budget social security systems may have a material adverse effect on our business and results of operations.

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our product candidates or any future product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product for which we obtain marketing approval. Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or the ACA, was enacted, which, substantially changes the way healthcare is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The ACA, among other things, subjects biologic products to potential competition by lower-cost biosimilars, addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increases the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program, extends the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjects manufacturers to new annual fees and taxes for certain branded prescription drugs, creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% (as of 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer’s outpatient drugs to be covered under Medicare Part D, and provides incentives to programs that increase the federal government’s comparative effectiveness research.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, various portions of the ACA are currently undergoing legal and constitutional challenges in the Fifth Circuit Court and the United States Supreme Court, and the Trump Administration has issued various Executive Orders that eliminated cost sharing subsidies and various provisions that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Additionally, Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended. We cannot predict what affect further changes to the ACA would have on our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation’s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and will remain in effect through 2029 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration’s budgets for fiscal years 2019 and 2020 contain further drug price control measures that could be enacted in future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Additionally, the Trump administration released a “Blueprint” to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The U.S. Department of Health and Human Services, or HHS, has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. This final rule codified

CMS's policy change that was effective January 1, 2019. Although a number of these, and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We expect that the healthcare reform measures that have been adopted and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product and could seriously harm our future revenues. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private third-party payors.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our drug product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Any denial in coverage or reduction in reimbursement from Medicare or other government programs may result in a similar denial or reduction in payments from private payors, which may adversely affect our future profitability.

Inadequate funding for the FDA and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future shutdowns of other government agencies, such as the SEC, may also impact our business through review of our public filings and our ability to access the public markets.

Any contamination in our manufacturing process, shortages of materials or failure of any of our key suppliers to deliver necessary components could result in interruption in the supply of our product candidates and delays in our clinical development or commercialization schedules.

Given the nature of biologics manufacturing, there is a risk of contamination in our manufacturing processes. Any contamination could materially adversely affect our ability to produce product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage.

Some of the materials required in our manufacturing process are derived from biologic sources. Such materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could materially and adversely affect our development timelines and our business, financial condition, results of operations and prospects.

Risks related to our business operations

Our gene therapy approach utilizes lentiviral vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Gene therapy remains a novel technology, with only a limited number of gene therapy products approved to date. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians specializing in the treatment of those diseases that our product candidates target prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments they are already familiar with and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, earlier gene therapy trials led to several well-publicized adverse events, including cases of leukemia, myelodysplastic syndromes and deaths seen in other trials using other vectors. Adverse events in our clinical studies, even if not ultimately attributable to our product candidates (such as the many adverse events that typically arise from the conditioning process), or adverse events in other lentiviral gene therapy trials, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team and key employees, including our Chief Executive Officer, Chief Financial Officer, President of Research and Development, Head of Operations, Chief Science Officer, Chief Business Officer, and General Counsel, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are “at will” employees. We do not maintain “key person” insurance policies on the lives of these individuals or the lives of any of our other employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives. Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or the loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives.

We will need to expand our operations and we may experience difficulties in managing this growth, which could disrupt our operations.

As of December 31, 2019, we had 85 full-time employees. As we mature, we expect to rapidly expand our full-time employee base and to hire more consultants and contractors. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.

If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources to manage our operations, continue our research and development activities and, in the longer term, build a commercial infrastructure to support commercialization of any of our product candidates that are approved for sale. Future growth would impose significant added responsibilities on members of management. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and product candidates requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas and to attract and retain sufficient numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development and growth goals.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA or of other foreign regulatory authorities, provide accurate information to the FDA and other foreign regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical studies, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We are subject to certain U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations. We can face serious consequences for violations.

Among other matters, U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations, which are collectively referred to as Trade Laws, prohibit companies and their employees, agents, clinical research organizations, legal counsel, accountants, consultants, contractors, and other partners from authorizing, promising, offering, providing, soliciting, or receiving directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. Violations of Trade Laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We also expect our non-U.S. activities to increase in time. We plan to engage third parties for clinical trials and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals and we can be held liable for the corrupt or other illegal activities of our personnel, agents, or partners, even if we do not explicitly authorize or have prior knowledge of such activities. The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the United States Foreign Corrupt Practices Act’s accounting provisions.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws health information privacy and security laws, and other health care laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations will be directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Health Care Program Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations. These laws will impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. The laws that will affect our operations include, but are not limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity can be found guilty of violating the statute without actual knowledge of the statute or specific intent to violate it. In addition, a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act, or FCA. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution;
- federal civil and criminal false claims laws and civil monetary penalty laws, including the FCA, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment to, or approval by Medicare, Medicaid, or other federal healthcare programs, knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or an obligation to pay or transmit money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. The FCA also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary’s selection of a particular supplier of items or services reimbursable by a federal or state governmental program;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information relating to the privacy, security and transmission of individually identifiable health information;
- the federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program to report annually to the U.S. Department of Health and Human Services information related to payments or other transfers of value made to physicians (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;

- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws described above, among others, some of which may be broader in scope and may apply regardless of the payor. Many U.S. states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare services reimbursed by any source, not just governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. There are ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement we could be subject to penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource-consuming and can divert a company's attention from the business.

The failure to comply with any of these laws or regulatory requirements subjects entities to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in significant civil, criminal and administrative penalties, damages, fines, disgorgement, individual imprisonment, exclusion from participation in federal and state funded healthcare programs (such as Medicare and Medicaid), contractual damages and the curtailment or restructuring of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws. Any action for violation of these laws, even if successfully defended, could cause a pharmaceutical manufacturer to incur significant legal expenses and divert management's attention from the operation of the business. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, that person or entity may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Prohibitions or restrictions on sales or withdrawal of future marketed products could materially affect business in an adverse way.

Efforts to ensure that our business arrangements will comply with applicable healthcare laws may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our candidates outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

Failure to comply with health and data protection laws and regulations could lead to government enforcement actions (which could include civil or criminal penalties), private litigation, and/or adverse publicity and could negatively affect our operating results and business.

We and any potential collaborators may be subject to federal, state, and foreign data protection laws and regulations (i.e., laws and regulations that address privacy and data security). In the United States, numerous federal and state laws and regulations, including federal health information privacy laws, state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act), that govern the collection, use, disclosure and protection of health-related and other personal information could apply to our operations or the operations of our collaborators. In addition, we may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA, as amended by HITECH. Depending on the facts and circumstances, we could be subject to civil, criminal, and administrative penalties if we knowingly obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

Compliance with U.S. and international data protection laws and regulations could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, or in some cases, impact our ability to operate in certain jurisdictions. Failure to comply with these laws and regulations could result in government enforcement actions (which could include civil, criminal and administrative penalties), private litigation, and/or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial patients, employees and other individuals about whom we or our potential collaborators obtain personal information, as well as the providers who share this information with us, may limit our ability to collect, use and disclose the information. Claims that we have violated individuals' privacy rights, failed to comply with data protection laws, or breached our contractual obligations, even if we are not found liable, could be expensive and time-consuming to defend and could result in adverse publicity that could harm our business.

European data collection is governed by restrictive regulations governing the use, processing and cross-border transfer of personal information.

In the event we decide to conduct clinical trials in the European Union, or EU, we may be subject to additional privacy restrictions. The collection and use of personal health data in the EU is governed by the provisions of the General Data Protection Regulation, or GDPR. This directive imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, notification of data processing obligations to the competent national data protection authorities and the security and confidentiality of the personal data. The GDPR also imposes strict rules on the transfer of personal data out of the European Union to the United States. Failure to comply with the requirements of the Data Protection Directive, the GDPR, and the related national data protection laws of the European Union Member States may result in fines and other administrative penalties. The GDPR introduces new data protection requirements in the European Union and substantial fines for breaches of the data protection rules. The GDPR regulations may impose additional responsibility and liability in relation to personal data that we process and we may be required to put in place additional mechanisms ensuring compliance with these and/or new data protection rules. This may be onerous and adversely affect our business, financial condition, prospects and results of operations.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates in clinical studies and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- the impairment of our business reputation;
- the withdrawal of clinical study participants;
- costs due to related litigation;
- the distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We carry master product liability insurance of $5.0 million per occurrence and $5.0 million in the aggregate in the United States. For Canada, we carry product liability insurance of CAD $10.0 million in the aggregate. For Australia, we carry product liability insurance of AUD $20.0 million in the aggregate. We believe our product liability insurance coverage is sufficient in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by certain of our product candidates are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life- threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our products, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Although we maintain workers’ compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the recent global financial crisis, could result in a variety of risks to our business, including weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payors or our collaborators. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business, financial condition, results of operations and prospects.

We or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite our security measures, our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. For example, in 2017 we were subjected to a cyberattack by a third party, which led to the theft of a portion of our funds. We implemented remedial measures promptly following this breach and do not believe that this breach had a material adverse effect on our business. In addition, in February 2019, one of our vendors was subject to a cyberattack by a third party, which resulted in the payment by us of a fraudulent invoice. We have implemented remedial measures following this breach and do not believe that this breach had a material effect on our business. However, if any cyberattack or data breach were to occur in the future and cause interruptions in our or our collaborators', contractors' or consultants' operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our business data, trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

Changes in tax law could adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations. We urge investors to consult with their legal and tax advisers regarding the implications of potential changes in tax laws on an investment in our common stock.

We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2019, we had federal and state net operating loss carryforwards of $121.8 million and $115.1 million, respectively, and federal and state research and development tax credit carryforwards of approximately $1.0 million and $0.2 million, respectively. If not utilized, the net operating loss carryforwards and research and development credits will generally expire at various dates through 2037 (other than federal net operating loss carryforwards generated in taxable years ending after December 31, 2017, which are not subject to expiration). These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. In addition, under Section 382 Internal Revenue of the Code of 1986, as amended, or the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be limited. We may have experienced ownership changes in the past. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurred or occurs and our ability to use our historical net operating loss and tax credit carryforwards is materially limited, or if our research and development carryforwards are adjusted, it would harm our future operating results by effectively increasing our future tax obligations.

Risks related to our intellectual property

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and *inter partes* reexamination proceedings before the U.S. Patent and Trademark Office, or USPTO, and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we or our licensors are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. In particular, we are aware of issued patents in the United States that cover the lentiviral vectors used in the manufacture of our product candidates. While we believe that we have reasonable defenses against a claim of infringement, potentially including that certain of these patents are expected to expire prior to commercializing our product candidates, if approved, in the United States, there can be no assurance that we will prevail in any such action by the holder of these patents. In the event that the holder of these patents seeks to enforce its patent rights and our defenses against a claim of infringement are unsuccessful, we may not be able to commercialize our product candidates in the United States, if approved, without first obtaining a license to some or all of these patents, which may not be available on commercially reasonable terms or at all. In addition, the defense of any claim of infringement, even if successful, is time-consuming, expensive and diverts the attention of our management from our ongoing business operations.

Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe or be alleged to infringe. In addition, third parties may obtain patents in the future and claim that use of our or our licensors' technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire.

Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure. Even in the absence of a finding of infringement, we may choose to obtain a license, if such a license is available. A successful claim of patent or other intellectual property infringement against us could materially adversely affect our business, results of operations and financial condition.

Our rights to develop and commercialize our product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.

We depend upon the intellectual property rights granted to us under licenses from third parties that are important or necessary to the development of our technology and products, including technology related to our manufacturing process and our gene therapy product candidates. In particular, we have in-licensed certain intellectual property rights and know-how from the University Health Network (relevant to AVR-RD-01 and our Fabry program) and affiliates of Lund University (relevant to AVR-RD-02 and our Gaucher program). In addition, we have in-licensed patents and patent applications from BioMarin Pharmaceutical Inc., or BioMarin (relevant to AVR-RD-03 and our Pompe program), and GenStem Therapeutics, Inc., or GenStem (relevant to AVR-RD-04 and our cystinosis program), directed to compositions and methods related to the manufacture and use of AVR-RD-03 and AVR-RD-04, respectively. Any termination of these licenses could result in the loss of significant rights and could harm or prevent our ability to commercialize our product candidates.

Each of our existing licenses are exclusive but are limited to particular fields, such as Fabry disease, Gaucher disease, Pompe disease, or cystinosis, and are subject to certain retained rights. Absent an amendment or additional agreement, we may not have the right to use intellectual property in-licensed for one of our programs for another program. In addition, licenses that we may enter into in the future may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories included in all of our licenses. Licenses to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business and financial condition.

In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. For example, pursuant to each of our intellectual property licenses with GenStem, BioMarin, and the rights holders associated with Lund University, our licensors retain control of such activities. Therefore, we cannot be certain that these patents and applications will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If our licensors fail to maintain such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected.

Our current license agreements impose, and we expect that future license agreements that we may enter into will impose, various obligations, including diligence and certain payment obligations. If we fail to satisfy our obligations, the licensor may have the right to terminate the agreement. Disputes may arise between us and any of our licensors regarding intellectual property subject to such agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may impair the value of the arrangement to us. Any such dispute could have a material adverse effect on our business. If we cannot maintain a necessary license agreement or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected product candidates.

If we are unable to obtain and maintain patent protection for our product candidates, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our product candidates may be adversely affected.

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on manufacturing and other know-how, patents, trade secrets, trademarks, license agreements and contractual provisions to establish our intellectual property rights and protect our products. These legal means, however, afford only limited protection and may not adequately protect our rights. The failure to obtain, maintain, enforce or defend such intellectual property rights, for any reason, could allow third parties to make competing products or impact our ability to develop, manufacture and market our products, if approved, on a commercially viable basis, or at all, which could have a material adverse effect on our financial condition and results of operations.

In particular, we rely primarily on trade secrets, know-how and other unpatented technology, which are difficult to protect. Although we seek such protection in part by entering into confidentiality agreements with our vendors, employees, consultants and others who may have access to proprietary information, we cannot be certain that these agreements will not be breached, adequate remedies for any breach would be available or our trade secrets, know-how and other unpatented proprietary technology will not otherwise become known to or be independently developed by our competitors. If we are unsuccessful in protecting our intellectual property rights, sales of our products may suffer and our ability to generate revenue could be severely impacted.

Our licensors and we have sought, and we intend to continue to seek to protect our proprietary position by filing patent applications in the United States and, in at least some cases, one or more countries outside the United States related to current and future product candidates that are important to our business. However, we cannot predict whether the patent applications we and our licensors are currently pursuing will issue as patents, whether the claims of any issued patents will provide us with a competitive advantage, or whether we will be able to successfully pursue patent applications in the future related to our current or future product candidates. While we have in-licensed patents and patent applications relevant to AVR-RD-03, we currently have no owned or in-licensed patents or patent applications covering AVR-RD-01 or AVR-RD-02, and the patent application that we in-licensed related to AVR-RD-04 is at a very early stage. Many of our product candidates are in-licensed from third parties. Accordingly, in some cases, the availability and scope of potential patent protection is limited based on prior decisions by our licensors or the inventors, such as decisions on when to file patent applications or whether to file patent applications at all.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. Although our license agreements grant us worldwide rights, and our currently in-licensed U.S. patent rights have certain corresponding foreign patents or patent applications, there can be no assurance that we will obtain or maintain such corresponding patents or patent applications with respect to any future license agreements. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States even in jurisdictions where we and our licensors pursue patent protection. Consequently, we and our licensors may not be able to prevent third parties from practicing our inventions in all countries outside the United States, even in jurisdictions where we and our licensors pursue patent protection, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we and our licensors have not pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights, even if obtained, in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court. We may not be able to protect our trade secrets in court.

If one of our licensing partners or we initiate legal proceedings against a third-party to enforce a patent covering one of our product candidates, should such a patent issue, the defendant could counterclaim that the patent covering our product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *inter partes* review and equivalent proceedings in foreign jurisdictions. Such proceedings could result in the revocation or cancellation of or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensing partners were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our product candidates. Such a loss of patent protection could have a material adverse impact on our business.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Certain of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management. Our licensors may face similar risks, which could have an adverse impact on intellectual property that is licensed to us.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property.

We may be subject to claims challenging the inventorship or ownership of the patents and other intellectual property that we own or license.

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an ownership interest in the patents and intellectual property that we own or license or that we may own or license in the future. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own; our licensors may face similar obstacles. We could be subject to ownership disputes arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against any claims challenging inventorship or ownership. If we or our licensors fail in defending any such claims, we may have to pay monetary damages and may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property, which could adversely impact our business, results of operations and financial condition.

Some intellectual property which we have in-licensed may have been discovered through government funded programs and thus may be subject to federal regulations such as "march-in" rights, certain reporting requirements, and a preference for U.S. industry. Compliance with such regulations may limit our exclusive rights, and limit our ability to contract with non-U.S. manufacturers.

Some of the intellectual property rights we have licensed, including rights licensed to us by GenStem, may have been generated through the use of U.S. government and California state funding and may therefore be subject to certain federal and state laws and regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). The U.S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. To the extent any of our current or future intellectual property is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply. Any exercise by the government of certain of its rights could harm our competitive position, business, financial condition, results of operations and prospects. With respect to state funding, specifically funding via the California Institute of Regenerative Medicine, or CIRM, which has granted funds for the study of AVR-RD-04 for cystinosis, the grantee has certain obligations and the state or CIRM has certain rights. For example, the grantee has an obligation to share intellectual property, including research results, generated by CIRM-funded research, for research use in California.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

Changes in either the patent laws or the interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes several significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted and also may affect patent litigation. These also include provisions that switched the United States from a “first-to-invent” system to a “first-to-file” system, allow third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent by the USPTO administered post grant proceedings. Under a first-to-file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

The patent positions of companies engaged in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Two cases involving diagnostic method claims and “gene patents” have recently been decided by the Supreme Court of the United States, or Supreme Court. On March 20, 2012, the Supreme Court issued a decision in Mayo Collaborative Services v. Prometheus Laboratories, Inc., or Prometheus, a case involving patent claims directed to a process of measuring a metabolic product in a patient to optimize a drug dosage for the patient. According to the Supreme Court, the addition of well-understood, routine or conventional activity such as “administering” or “determining” steps was not enough to transform an otherwise patent-ineligible natural phenomenon into patent-eligible subject matter. On July 3, 2012, the USPTO issued a guidance memo to patent examiners indicating that process claims directed to a law of nature, a natural phenomenon or a naturally occurring relation or correlation that do not include additional elements or steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to not patent-eligible subject matter. On June 13, 2013, the Supreme Court issued its decision in Association for Molecular Pathology v. Myriad Genetics, Inc., or Myriad, a case involving patent claims held by Myriad Genetics, Inc. relating to the breast cancer susceptibility genes BRCA1 and BRCA2. Myriad held that an isolated segment of naturally occurring DNA, such as the DNA constituting the BRCA1 and BRCA2 genes, is not patent-eligible subject matter, but that complementary DNA, which is an artificial construct that may be created from RNA transcripts of genes, may be patent-eligible. On March 4, 2014, the USPTO issued a guidance memorandum to patent examiners entitled 2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of Nature/Natural Principles, Natural Phenomena, And/Or Natural Products. These guidelines instruct USPTO examiners on the ramifications of the Prometheus and Myriad rulings and apply the Myriad ruling to natural products and principles including all naturally occurring nucleic acids.

Certain claims of our licensed patents and patent applications contain, and any future patents we may obtain may contain, claims that relate to specific recombinant DNA sequences that are naturally occurring at least in part and, therefore, could be the subject of future challenges made by third parties. In addition, the 2014 USPTO guidance could impact our ability to pursue similar patent claims in patent applications we may prosecute in the future.

We cannot assure you that our efforts to seek patent protection for our product candidates will not be negatively impacted by the decisions described above, rulings in other cases or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact the Supreme Court’s decisions in Prometheus and Myriad may have on the ability of life science companies to obtain or enforce patents relating to their products in the future. These decisions, the guidance issued by the USPTO and rulings in other cases or changes in USPTO guidance or procedures could have a material adverse effect on our existing patent rights and our ability to protect and enforce our intellectual property in the future.

Moreover, although the Supreme Court has held in Myriad that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene-related patent claims, and we may deem it necessary to defend ourselves against these claims by asserting non-infringement and/or invalidity positions, or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be subjected to an injunction that would prevent us from utilizing the patented subject matter. Such outcomes could harm our business, financial condition, results of operations or prospects.

If we do not obtain patent term extension and data exclusivity for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of our product candidates, one or more U.S. patents that we license or may own or license in the future, if any, may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. A patent may only be extended once and only based on a single approved product. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially. In addition, we do not control the efforts of our licensors to obtain a patent term extension, and there can be no assurance that they will pursue or obtain such extensions to the patents that we license from them.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

We have pending trademark applications with the USPTO for the marks "plato" and "AVROBIO" but do not have trademarks or trademark applications with the USPTO for the marks "AVRO" or the AVROBIO logo. In the future, even if we apply for registration of these marks, there can be no assurance that such registration will be approved. Once registered, our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

Intellectual property rights and regulatory exclusivity rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make gene therapy products that are similar to our product candidates but that are not covered by the claims of the patents that we license or may own or license in the future;
- we, our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patents or pending patent applications that we license or may own or license in the future;
- we, our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;

- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our pending licensed patent applications or those that we may own or license in the future will not lead to issued patents;
- issued patents that we hold rights to or may hold rights to in the future may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- one or more of our product candidates may never be protected by patents;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may have an adverse effect on our business; and
- we may choose not to file a patent application for certain trade secrets or know-how, and a third party may subsequently file a patent application or obtain a patent covering such intellectual property.

Should any of these events occur, they could significantly harm our business, financial condition, results of operations and prospects.

Risks related to ownership of our common stock

The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above the price at which you purchased our shares.

Our stock price is likely to be volatile. Since our initial public offering, or IPO, in June 2018, through March 6, 2020, the trading price of our common stock has ranged from $11.85 to $53.70. The stock market in general, and the market for biopharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above the price at which you purchased shares. The market price for our common stock may be influenced by many factors, including:

- adverse results or delays in preclinical studies or clinical trials;
- reports of adverse events in other gene therapy products or clinical studies of such products;
- an inability to obtain additional funding;
- failure by us to successfully develop and commercialize our product candidates;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- the introduction of new products, services or technologies by our competitors;
- failure by us to meet or exceed financial projections we may provide to the public;
- failure by us to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;

- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- the trading volume of our common stock.

In addition, companies trading in the stock market in general, and The Nasdaq Global Select Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

An active trading market for our common stock may not be sustained.

Prior to our IPO in June 2018, there had been no public market for our common stock. Although our common stock is listed on The Nasdaq Global Select Market, an active trading market for our shares may never be sustained. If an active market for our common stock is not sustained, it may be difficult for you to sell shares you purchased without depressing the market price for the shares, or at all.

An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling additional shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our common stock will likely depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. Although we have obtained research coverage from certain analysts, there can be no assurance that analysts will continue to cover us or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, our share price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Based on shares outstanding as of March 6, 2020, our executive officers, directors, five percent stockholders and their affiliates beneficially owned approximately 28% of our voting stock. As a result, if these stockholders were to act together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these stockholders, acting together, may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders. Some of these persons or entities may have interests different than yours. For example, because many of these stockholders purchased their shares at prices substantially below the current trading price of our stock and have held their shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other stockholders.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," or EGC, as defined in the JOBS Act. We will remain an EGC until the earliest of: (i) the last day of the fiscal year in which we have total annual gross revenues of $1.07 billion or more; (ii) the last day of the fiscal year following the fifth anniversary of the date of the completion of our IPO; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC, which means the first day of the year following the first year in which the market value of our common stock that is held by non-affiliates exceeds $700 million as of June 30. For so long as we remain an EGC, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, or Section 404;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's discussion and analysis of financial condition and results of operations" disclosure;
- reduced disclosure obligations regarding executive compensation; and
- an exemption from the requirement to seek nonbinding advisory votes on executive compensation or golden parachute arrangements.

We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of reduced reporting burdens in this report. In particular, we have not included in this report, and do not intend to include in our 2020 annual proxy statement, all of the executive compensation information that would be required if we were not an EGC. We cannot predict whether investors will find our common stock less attractive if we rely on certain or all of these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act provides that an EGC may take advantage of an extended transition period for complying with new or revised accounting standards. This allows an EGC to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will not be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company" if the market value of our common stock held by non-affiliates is below $250 million (or $700 million if our annual revenue is less than $100 million) as of June 30 in any given year, which would allow us to take advantage of many of the same exemptions from disclosure requirements.

We expect to continue to incur increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives.

As a public company, and particularly after we are no longer an EGC, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and will continue to make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and increasingly more expensive for us to obtain and maintain director and officer liability insurance.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting, and, once we are no longer an EGC or a "smaller reporting company", we will be required to furnish an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404, we continue to be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially continue to engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our stock.

We are required to disclose changes made in our internal controls and procedures on a quarterly basis and our management is required to assess the effectiveness of these controls annually. However, for as long as we are an EGC or a "smaller reporting company", our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control over financial reporting pursuant to Section 404. We could be an EGC for up to five years following the completion of our IPO and will qualify as a "smaller reporting company" if the market value of our common stock held by non-affiliates is below $250 million (or $700 million if our annual revenue is less than $100 million) as of June 30 in any given year. An independent assessment of the effectiveness of our internal control over financial reporting could detect problems that our management's assessment might not. Undetected material weaknesses in our internal control over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation.

We and our independent registered public accounting firm have identified material weaknesses in our internal control over financial reporting. While we have taken numerous steps to address these material weaknesses and believe we have made progress toward remediating them, if we are unable to remedy these material weaknesses, or if we fail to establish and maintain effective internal controls, we may be unable to produce timely and accurate financial statements, and we may conclude that our internal control over financial reporting is not effective, which could adversely impact our investors' confidence and our stock price.

In our Annual Report on Form 10-K for the year ended December 31, 2018, we reported material weaknesses in our internal control over financial reporting related to deficiencies in our controls over the financial statement close process, including over complex accounting issues, expense classification and accrued research and development expenses, as well as the cash disbursement process. During 2019, we took a number of actions, including the efforts outlined in Item 9A of this Annual Report on Form 10-K, designed to improve our internal control over financial reporting to remediate these material weaknesses.

We believe significant progress was made in 2019 to enhance and strengthen our internal control over financial reporting. However, while we believe our internal controls were properly designed and implemented as of December 31, 2019, they were not in all cases in place for a sufficient period of time to demonstrate operating effectiveness as of December 31, 2019. As a result, management has concluded that the material weaknesses were not fully remediated as of December 31, 2019.

We expect to continue our efforts to improve our control processes, though there can be no assurance that our efforts will ultimately be successful or avoid potential future material weaknesses, and we expect to continue incurring additional costs as a result of these efforts. Management remains committed to the implementation of remediation efforts to address these material weaknesses. If we are unable to successfully remediate our existing or any future material weaknesses in our internal control over financial reporting, or if we identify any additional material weaknesses, the accuracy and timing of our financial reporting may be adversely affected, we may be unable to maintain compliance with securities law requirements regarding timely filing of periodic reports in addition to applicable stock exchange listing requirements, investors may lose confidence in our financial reporting, and our stock price may decline as a result. We also could become subject to investigations by Nasdaq, the SEC or other regulatory authorities.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly.

Sales of a substantial number of shares of our common stock in the public market could occur at any time, subject to certain restrictions described below. These sales, or the perception in the market that holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. As of March 6, 2020, holders of an aggregate of approximately 4.5 million shares of our common stock will have rights, subject to certain conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. In addition, 3,414,445 shares reserved for issuance upon the exercise of existing stock options outstanding as of December 31, 2019 under our equity incentive plans will become eligible for sale in the public market in the future. We have registered all shares of common stock that we may issue under our equity compensation plans, which can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

We do not intend to pay dividends on our common stock, so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock. For example, our prior loan facility with Silicon Valley Bank restricted our ability to pay any dividends or making any distributions on account of our capital stock, and we may enter into agreements in the future with similar restrictions. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Our amended and restated certificate of incorporation, amended and restated by-laws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and by-laws, include provisions that:

- authorize “blank check” preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors, the chairperson of our board of directors, our chief executive officer or our president;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;

- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated by-laws; and require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our bylaws contain exclusive forum provisions, which may limit a stockholder's ability to bring a claim in a judicial forum it finds favorable and may discourage lawsuits with respect to such claims.

Our amended and restated bylaws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any state law claim for (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of or based on a fiduciary duty owed by any of our current or former directors, officers or other employees to us or our stockholders; (3) any action asserting a claim against us or any of our current or former directors, officers, employees or stockholders arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws; or (4) any action asserting a claim governed by the internal affairs doctrine (the "Delaware Forum Provision"). The Delaware Forum Provision will not apply to any causes of action arising under the Securities Act of 1933 or the Securities Exchange Act of 1934. Our amended and restated bylaws further provide that, unless we consent in writing to an alternative forum, the United States District Court for the District of Massachusetts will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (the "Federal Forum Provision"). We have chosen the United States District Court for the District of Massachusetts as the sole and exclusive forum for such Securities Act causes of action because our principal executive offices are located in Cambridge, Massachusetts. In addition, our amended and restated bylaws provide that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock is deemed to have notice of and consented to the foregoing Delaware Forum Provision and the Federal Forum Provision.

On December 19, 2018, in *Sciabacucchi v. Salzberg*, C.A. No. 2017-0931-JTL (Del. Ch.), the Court of Chancery of the State of Delaware issued a decision declaring that federal forum selection provisions that purport to require claims under the Securities Act be brought in federal court are ineffective and invalid under Delaware law. In August 2019, the decision was appealed to the Delaware Supreme Court, and the appeal remains pending before the Delaware Supreme Court. Unless and until the Court of Chancery's decision in *Sciabacucchi* is reversed by the Delaware Supreme Court or otherwise abrogated, we do not intend to enforce our Federal Forum Provision designating the District of Massachusetts as the exclusive forum for Securities Act claims. In the event that the Delaware Supreme Court affirms the Court of Chancery's *Sciabacucchi* decision or otherwise makes a determination that provisions such as the Federal Forum Provision are invalid, our Board of Directors intends to amend promptly our bylaws to remove the Federal Forum Provision. Such amendment could cause us to incur additional costs, which could have an adverse effect on our business, financial condition or results of operations.

We recognize that the Delaware Forum Provision and the Federal Forum Provision may impose additional litigation costs on stockholders who assert the provision is not enforceable and may impose more general additional litigation costs in pursuing any such claims, particularly if the stockholders do not reside in or near the State of Delaware or the Commonwealth of Massachusetts. Additionally, these forum selection clauses in our amended and restated bylaws may limit our stockholders' ability to bring a claim in a judicial forum that they find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees even though an action, if successful, might benefit our stockholders. The Federal Forum Provision may also impose additional litigation costs on stockholders who assert the provision is not enforceable. The Court of Chancery of the State of Delaware and the United States District Court for the District of Massachusetts may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters are located in Cambridge, Massachusetts. Our current leased facility for our corporate headquarters encompasses approximately 11,218 square feet of office space. The lease for this facility expires in January 2023. In August 2018, we entered into a sub-lease for 13,643 square feet of laboratory space located in Cambridge Massachusetts, which expires in October 2020.

Item 3. Legal Proceedings

From time to time, we are subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Although the results of litigation and claims cannot be predicted with certainty, as of the date of this Annual Report on Form 10-K, we do not believe we are party to any claim or litigation the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for the Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our common stock is traded on the Nasdaq Global Select Market under the symbol "AVRO". Trading of our common stock commenced on June 21, 2018, following the completion of our initial public offering. Prior to that time, there was no established public trading market for our common stock.

As of March 6, 2020, the number of holders of record of our common stock was 9. This number does not include beneficial owners whose shares are held in street name.

Dividends

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our board of directors and will depend on, among other factors, our results of operations, financial condition, capital requirements, contractual restrictions, business prospects and other factors our board of directors may deem relevant. Investors should not purchase our common stock with the expectation of receiving cash dividends.

Equity Compensation Plans

The information required by Item 5 of Form 10-K regarding equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report.

Issuer Purchases of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

We did not sell any unregistered equity securities during the period covered by this Annual Report on Form 10-K.

Use of Proceeds from Initial Public Offering of Common Stock

On June 25, 2018, we completed our initial public offering of 6,035,151 shares of our common stock at a price of $19.00 per share for an aggregate offering price of approximately $114.7 million, including the full exercise of the underwriters' option to purchase additional shares. Morgan Stanley & Co. LLC, Cowen and Company, LLC, Wells Fargo Securities, LLC and Wedbush Securities Inc. served as the underwriters of the IPO. The offer and sale of all of the shares in the offering were registered under the Securities Act pursuant to a registration statement on Form S-1 (File Nos. 333-225213 and 333-225764), which became effective on June 20, 2018.

We received aggregate net proceeds from the offering of approximately $104.0 million, after deducting underwriting discounts and commissions, as well as other offering expenses. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning ten percent or more of any class of our equity securities or to any other affiliates.

As of December 31, 2019, we had used approximately $97.5 million of the net proceeds from the IPO, primarily to fund our current programs in Fabry disease, Gaucher disease, cystinosis, and Pompe disease; our external and internal manufacturing and process development activities related to our programs and to fund research and development activities that relate to all of our clinical and preclinical activities, including the cost of research and development personnel; and general and administrative expenses, working capital and other general corporate purposes. There has been no material change in our planned use of the net proceeds from the offering as described in the final prospectus filed with the SEC pursuant to Rule 424(b) under the Securities Act.

Item 6. Selected Financial Data

Not Applicable.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

Our management's discussion and analysis of our financial condition and results of operations are based upon our consolidated financial statements included in this Annual Report on Form 10-K, which have been prepared by us in accordance with United States generally accepted accounting principles, or GAAP, and with Regulation S-X promulgated under the Securities Exchange Act of 1934, as amended. This discussion and analysis should be read in conjunction with the consolidated financial statements and the notes thereto included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in Part I, Item 1A. Risk Factors of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a leading clinical-stage gene therapy company with a mission to free people from a lifetime of genetic disease. Our company is focused on developing potentially curative *ex vivo* lentiviral-based gene therapies to treat patients with rare diseases following a single dose treatment regimen. Our gene therapies employ hematopoietic stem cells that are harvested from the patient and then modified with a lentiviral vector to insert the equivalent of a functional copy of the gene that is defective in the target disease. We believe that our approach, which is designed to transform stem cells from patients into therapeutic products, has the potential to provide curative benefit for a range of diseases. Our initial focus is on a group of rare genetic diseases referred to as lysosomal diseases, some of which today are primarily managed with enzyme replacement therapies, or ERTs. These lysosomal diseases have well-understood biologies, identified patient populations, established standards of care yet with significant unmet needs, and represent large market opportunities with approximately $4.0 billion in worldwide net sales in 2019.

Our initial pipeline is comprised of four lentiviral-based gene therapy programs, including AVR-RD-01 for the treatment of Fabry disease, AVR-RD-04 for the treatment of cystinosis, AVR-RD-02 for the treatment of Gaucher disease and AVR-RD-03 for the treatment of Pompe disease. AVR-RD-01 is currently being evaluated in an investigator-sponsored Phase 1 clinical trial and a company-sponsored Phase 2 clinical trial. Five patients have been dosed in the investigator-sponsored Phase 1 clinical trial of AVR-RD-01, and enrollment is complete. As of March 6, 2020, four patients have been dosed in our company-sponsored Phase 2 clinical trial of AVR-RD-01, and we are actively recruiting additional potential patients for our currently active sites in Australia, Canada and the United States. AVR-RD-04 is currently being studied by our collaborators at the University of California, San Diego, or UCSD, in a Phase 1/2 investigator-sponsored clinical trial, and as of March 6, 2020 one patient has been dosed. In January 2020, we announced that we received notice of clearance from the U.S. Food and Drug Administration, or FDA, regarding an Investigational New Drug, or IND, application for AVR-RD-02, our investigational gene therapy for the treatment of Gaucher disease. The Phase 1/2 clinical trial for AVR-RD-02 is actively recruiting in Australia and Canada, with additional sites planned in the United States. Our AVR-RD-03 program for Pompe disease is currently in preclinical development with the first IND-enabling preclinical study initiated in 2019.

Since our inception in 2015, we have devoted substantially all of our resources to organizing and staffing our company, business planning, raising capital, acquiring or discovering product candidates and securing related intellectual property rights, conducting discovery, research and development activities for our programs and planning for potential commercialization. We do not have any products approved for sale and have not generated any revenue from product sales. To date, we have funded our operations with proceeds from the sales of preferred stock and our initial public offering, or IPO, and we have raised additional capital through an underwritten public offering that closed in July 2019, or the July 2019 Follow-On Offering, and an underwritten public offering that closed in February 2020, or the February 2020 Follow-On Offering. Through December 31, 2019, we had received gross cash proceeds of $87.5 million from sales of our preferred stock, and gross cash proceeds, before deducting underwriting discounts and commissions and expenses, of $114.7 million and $138.3 million from sales of our common stock through our IPO and July 2019 Follow-On Offering, respectively. Since our inception, we have incurred significant operating losses. Our ability to generate product revenue sufficient to achieve profitability will depend heavily on the successful development and eventual commercialization of one or more of our current or future product candidates and programs. Our net losses were $73.0 million and $46.4 million for the years ended December 31, 2019 and 2018, respectively. As of December 31, 2019, we had an accumulated deficit of $144.7 million. We expect to continue to incur significant expenses for at least the next several years as we advance our current and future product candidates from discovery through preclinical development and clinical trials and seek regulatory approval of our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. We may also incur expenses in connection with the in-licensing or acquisition of additional product candidates. Furthermore, we expect to continue incurring additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations with proceeds from outside sources, with a majority of such proceeds to be derived from sales of equity, including the net proceeds from our IPO and follow-on offerings. We also plan to pursue additional funding from outside sources, including our expansion of, or our entry into, new borrowing arrangements; research and development incentive payments from the Australian government; and our entry into potential future collaboration agreements for one or more of our programs. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more of our product candidates or delay our pursuit of potential in-licenses or acquisitions.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2019, we had cash and cash equivalents of $187.0 million. We believe that our existing cash and cash equivalents as of December 31, 2019, together with the estimated net proceeds of $93.5 million from our February 2020 Follow-on Offering, will enable us to fund our operating expenses and capital expenditure requirements into the second quarter of 2022. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. See "—Liquidity and Capital Resources." To finance our operations beyond that point, we will need to raise additional capital, which cannot be assured.

Components of Our Consolidated Results of Operations

Revenue

We have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products in the near future. If development efforts for our product candidates are successful and result in regulatory approval or additional license agreements with third parties, we may generate revenue in the future from product sales.

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred in connection with the discovery and development of our product candidates. We expense research and development costs as incurred. These expenses consist of costs incurred in connection with the development of our product candidates, including:

- license maintenance fees and milestone fees incurred in connection with various license agreements;
- expenses incurred under agreements with contract research organizations, or CROs, contract manufacturing organizations, or CMOs, as well as investigative sites and consultants that conduct our clinical trials, preclinical studies and other scientific development services;
- manufacturing scale-up expenses and the cost of acquiring and manufacturing preclinical and clinical trial materials and commercial materials, including manufacturing validation batches;
- employee-related expenses, including salaries, related benefits, travel and stock-based compensation expense for employees engaged in research and development functions;
- costs related to compliance with regulatory requirements; and
- allocated facilities costs, depreciation and other expenses, which include rent and utilities.

We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers.

Our direct research and development expenses are tracked on a program-by-program basis for our product candidates and consist primarily of external costs, such as fees paid to outside consultants, CROs, CMOs, and central laboratories in connection with our preclinical development, process development, manufacturing and clinical development activities. Our direct research and development expenses by program also include fees incurred under license agreements. We do not allocate employee costs or facility expenses, including depreciation or other indirect costs, to specific programs because these costs are deployed across multiple programs and, as such, are not separately classified. We use internal resources primarily to oversee the research and discovery as well as for managing our preclinical development, process development, manufacturing and clinical development activities. These employees work across multiple programs and, therefore, we do not track their costs by program.

We have modified the presentation within the following tables to include expenses related to other preclinical development activities outside of our already presented programs in our direct research and development expenses, which were previously included as other unallocated research and development expenses. We have adjusted prior period amounts to reflect the changes in presentation made in the current period. The table below summarizes our research and development expenses incurred by program (in thousands):

	Year Ended December 31,	
	2019	2018
Fabry	$ 9,833	$ 10,673
Gaucher	6,591	7,503
Pompe	5,722	1,007
Cystinosis	4,177	1,241
Other	4,451	763
Unallocated research and development expenses	24,200	13,908
Total research and development expenses	$ 54,974	$ 35,095

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. As a result, we expect that our research and development expenses will increase substantially over the next several years, particularly as we increase personnel costs, including stock-based compensation, contractor costs and facilities costs, as we continue to advance the development of our product candidates. We also expect to incur additional expenses related to milestone and royalty payments payable to third parties with whom we have entered into license agreements to acquire the rights to our product candidates.

The successful development and commercialization of our product candidates is highly uncertain. At this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to complete the preclinical and clinical development of any of our product candidates or when, if ever, material net cash inflows may commence from any of our product candidates. This uncertainty is due to the numerous risks and uncertainties associated with product development and commercialization, including the uncertainty of:

- the scope, progress, outcome and costs of our preclinical development activities, clinical trials and other research and development activities;
- establishing an appropriate safety profile with IND-enabling studies;
- successful patient enrollment in, and the design, initiation and completion of, clinical trials;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- development and timely delivery of commercial-grade drug formulations that can be used in our clinical trials and for commercial launch;
- obtaining, maintaining, defending and enforcing patent claims and other intellectual property rights;
- significant and changing government regulation;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with others;
- maintaining a continued acceptable safety profile of the product candidates following approval; and
- the risks disclosed in the section entitled “Risk Factors” of this Annual Report on Form 10-K.

We may never succeed in achieving regulatory approval for any of our product candidates. We may obtain unexpected results from our clinical trials. We may elect to discontinue, delay or modify clinical trials of some product candidates or focus on others. Any changes in the outcome of any of these variables with respect to the development of our product candidates in preclinical and clinical development could mean a significant change in the costs and timing associated with the development of these product candidates. For example, if the FDA, or another regulatory authority were to delay our planned start of clinical trials or require us to conduct clinical trials or other testing beyond those that we currently expect, or if we experience significant delays in enrollment in any of our planned clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development of that product candidate. Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries, related benefits, travel and stock-based compensation expense for personnel in executive, finance and administrative functions. General and administrative expenses also include professional fees for legal, consulting, accounting and audit services.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research activities and development of our product candidates. We also anticipate that we will continue to incur increased accounting, audit, legal, regulatory, compliance, director and officer insurance costs as well as investor and public relations expenses associated with being a public company. We anticipate the additional costs for these services will substantially increase our general and administrative expenses. Additionally, if and when we believe a regulatory approval of a product candidate appears likely, we anticipate an increase in payroll and other commercialization-related expenses as a result of our preparation for commercial operations, especially as it relates to the sales and marketing of our product candidate.

Other Income (Expense)

Interest Income

Interest income consists of interest earned on money market funds and other bank deposits.

Other Expense

Other expense consists of foreign exchange gain or loss.

Change in Fair Value of Preferred Stock Warrant Liability

In connection with entering into a loan agreement, or the Loan Agreement, with Silicon Valley Bank, or SVB, in 2017, we agreed to issue a warrant to purchase shares of our preferred stock to SVB. Prior to the completion of our IPO, we classified the warrant as a liability on our consolidated balance sheet and we were required to remeasure to fair value at each reporting date. We recognized changes in the fair value of the warrant liability as a component of other income (expense), net in our consolidated statements of operations and comprehensive loss. On June 21, 2018, in connection with our IPO, the warrant to purchase preferred stock was converted to a warrant to purchase common stock. The carrying amount of the warrant to purchase preferred stock as of the date of our IPO was transferred to additional paid in capital. No further revaluation is needed for the warrant to purchase common stock.

Change in Fair Value of Derivative Liability

Our stock purchase agreement with University Health Network, or UHN, provides for a payment to UHN upon completion of an initial public offering, which included our IPO, if UHN’s fully-diluted percentage ownership of our company is reduced within a range of specified percentages. We classified the IPO dilution payment obligation as a liability on our consolidated balance sheet and we were required to remeasure to fair value at each reporting date. We recognized changes in the fair value of the derivative liability as a component of other income (expense), net in our consolidated statements of operations and comprehensive loss. On June 21, 2018, in connection with our IPO, we remeasured the fair value of the derivative liability to $2.0 million as we were required to pay the dilution payment as mentioned above, which was paid in July 2018.

Consolidated Results of Operations

Comparison of the Years Ended December 31, 2019 and 2018

The following table summarizes our consolidated results of operations for the years ended December 31, 2019 and 2018 (in thousands):

	Year Ended December 31,		
	2019	**2018**	**Change**
Operating expenses:			
Research and development	$ 54,974	$ 35,095	$ 19,879
General and administrative	20,835	11,148	9,687
Total operating expenses	75,809	46,243	29,566
Loss from operations	(75,809)	(46,243)	(29,566)
Other income (expense):			
Interest income	2,934	1,726	1,208
Change in fair value of preferred stock warrant liability	—	(162)	162
Change in fair value of derivative liability	—	(1,629)	1,629
Other expense	(90)	(53)	(37)
Total other income (expense), net	2,844	(118)	2,962
Net loss	$ (72,965)	$ (46,361)	$ (26,604)

Research and Development Expenses

The following table summarizes our research and development expenses incurred during the years ended December 31, 2019 and 2018 (in thousands):

	Year Ended December 31,		
	2019	**2018**	**Change**
Direct research and development expenses by program:			
Fabry	$ 9,833	$ 10,673	$ (840)
Gaucher	6,591	7,503	(912)
Pompe	5,722	1,007	4,715
Cystinosis	4,177	1,241	2,936
Other	4,451	763	3,688
Unallocated research and development expenses:			
Personnel related (including stock-based compensation)	16,733	9,297	7,436
Other	7,467	4,611	2,856
Total research and development expenses	$ 54,974	$ 35,095	$ 19,879

Research and development expenses were $55.0 million for the year ended December 31, 2019, compared to $35.1 million for the year ended December 31, 2018. The increase of $19.9 million was primarily due to increases of $4.7 million in direct costs related to our Pompe program, $3.7 million in direct costs related to our Other programs, $2.9 million in direct costs related to our Cystinosis program, and $10.3 million in unallocated research and development expenses, all partially offset by a decrease of $0.9 million in direct costs related to our Gaucher program and a decrease of $0.8 million in direct costs related to our Fabry program.

The increase in direct costs related to our Pompe program was primarily due to increases in preclinical and manufacturing costs of $4.7 million.

The increase in direct costs related to our Cystinosis program was primarily due to an increase in preclinical and clinical expenses of $1.6 million and a license fee payment of $2.0 million, partially off-set by decreases in consulting fees of $0.4 million, and manufacturing costs of $0.2 million.

The increase in direct costs related to our Other programs was primarily due to increases in preclinical and manufacturing costs of $3.7 million.

The increase in unallocated research and development expenses was primarily due to an increase of $7.4 million in personnel-related costs, including stock-based compensation as a result of hiring additional personnel in our research and development department, and an increase of $2.5 million in facility costs and rent expense. Personnel-related costs for the years ended December 31, 2019 and 2018 included stock-based compensation expense of $3.6 million and $0.9 million, respectively.

General and Administrative Expenses

General and administrative expenses were $20.8 million for the year ended December 31, 2019, compared to $11.1 million for the year ended December 31, 2018. The increase of $9.7 million was primarily due to increases of $5.2 million in personnel-related costs including stock-based compensation and $4.4 million in costs associated with being a publicly traded company, including $1.9 million in professional fees, $1.7 million in consulting expenses, and $0.8 million in insurance costs. The increase in personnel-related costs was due to the hiring of additional personnel in our general and administrative functions.

Other Income (Expense), net

Other income (expense), net was income of $2.8 million for the year ended December 31, 2019, compared to a net expense of $0.1 million for the year ended December 31, 2018. The increase of $3.0 million was primarily due to a $1.2 million increase in interest income and a decrease of $1.8 million due to the change in the fair value of the derivative liability and the preferred stock warrant liability.

Liquidity and Capital Resources

Since our inception, we have not generated any revenue and have incurred significant operating losses and negative cash flows from our operations. We have funded our operations to date primarily with proceeds from the sale of preferred stock and our common stock through our IPO, and we have raised additional capital through our July 2019 Follow-On Offering and our February 2020 Follow-On Offering. Through December 31, 2019, we had received gross cash proceeds of $87.5 million from sales of our preferred stock, and gross cash proceeds, before deducting underwriting discounts and commissions and expenses, of $114.7 million and $138.3 million from sales of our common stock through our IPO and July 2019 Follow-On Offering, respectively.

On July 1, 2019, we filed a shelf registration statement on Form S-3 with the SEC, or the July 2019 Shelf, which covers the offering, issuance and sale by us of up to an aggregate of $200.0 million of our common stock, preferred stock, debt securities, warrants and/or units. We simultaneously entered into a Sales Agreement with Cowen and Company, LLC, as sales agent, to provide for the offering, issuance and sale by us of up to $50.0 million of our common stock from time to time in “at-the-market” offerings under the July 2019 Shelf. The July 2019 Shelf was declared effective by the SEC on July 10, 2019.

On December 20, 2019, we filed a shelf registration statement on Form S-3 with the SEC, or the December 2019 Shelf, which covers the offering, issuance and sale by us of up to an aggregate of $250.0 million of our common stock, preferred stock, debt securities, warrants and/or units. The December 2019 Shelf was declared effective by the SEC on January 14, 2020.

In July 2019, we closed the July 2019 Follow-On Offering as an underwritten public offering under the July 2019 Shelf of 7,475,000 shares of our common stock at a public offering price of $18.50 per share, which included 975,000 shares of our common stock resulting from the full exercise of the underwriters’ option to purchase additional shares at the public offering price, less underwriting discounts and commissions. The net proceeds to us from this offering, after deducting underwriting discounts and commissions and other offering expenses payable by us, were approximately $129.5 million.

In February 2020, we closed the February 2020 Follow-On Offering as an underwritten public offering under the December 2019 Shelf of 4,350,000 shares of our common stock at a public offering price of $23.00 per share, less underwriting discounts and commissions. The net proceeds to us from this offering, after deducting underwriting discounts and commissions and other offering expenses payable by us, were approximately $93.5 million.

Cash in excess of immediate requirements is invested primarily with a view to liquidity and capital preservation.

Cash Flows

The following table summarizes our cash flows for each of the periods presented (in thousands):

	Year Ended December 31,	
	2019	2018
Net cash used in operating activities	$ (67,668)	$ (37,648)
Net cash used in investing activities	(1,585)	(1,832)
Net cash provided by financing activities	129,994	160,287
Net increase in cash, cash equivalents and restricted cash	$ 60,741	$ 120,807

Operating Activities

During the year ended December 31, 2019, operating activities used $67.7 million of cash and cash equivalents, resulting from our net loss of $73.0 million and net cash used by changes in our operating assets and liabilities of $2.2 million, offset in part by non-cash charges of $7.5 million. Net cash used by changes in our operating assets and liabilities for the year ended December 31, 2019 consisted primarily of a $4.9 million increase in prepaid expenses and other current assets and $0.2 million increase in other assets, partially offset by a $1.0 million increase in accounts payable and a $1.9 million increase in accrued expenses and other current liabilities. The increase in prepaid expenses and other current assets was primarily due to a $3.9 million increase in prepaid development costs, $0.6 million increase in prepaid insurance and a $0.6 million increase in tax incentive refund receivable from the Australian government.

During the year ended December 31, 2018, operating activities used $37.6 million of cash and cash equivalents, resulting from our net loss of $46.4 million, partially offset by non-cash charges of $4.6 million and net cash provided by changes in our operating assets and liabilities of $4.2 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2018 consisted primarily of a $5.3 million increase in accrued expenses and other current liabilities and a $2.0 million increase in accounts payable, partially offset by a $0.1 million increase in other assets and a $3.0 million increase in prepaid expenses and other current assets. The increases in accrued expenses and other current liabilities were primarily due to ongoing research, development, and clinical trial work, and an increase in the incentive bonus accrual as of December 31, 2018. The increase in prepaid expenses and other current assets was primarily due to a $0.8 million increase in prepaid development costs, a $1.3 million increase in tax incentive refund receivable from the Australian government and a $0.2 million increase in interest income receivable.

Investing Activities

During the years ended December 31, 2019 and 2018, we used $1.6 million and $1.8 million of cash and cash equivalents in investing activities consisting of purchases of property and equipment.

Financing Activities

During the year ended December 31, 2019, net cash provided by financing activities was $130.0 million, primarily consisting of net cash proceeds of $129.5 million from our July 2019 Follow-on Offering.

During the year ended December 31, 2018, net cash provided by financing activities was $160.3 million, primarily consisting of net cash proceeds of $104.0 million from our IPO proceeds and $58.3 million from our issuance of Series B preferred stock in January 2018.

Term Loan Agreement

In June 2017, we entered into the Loan Agreement with SVB providing a senior secured non-revolving loan facility of up to an aggregate principal amount of $10.0 million, available for us to draw down in three tranches until October 31, 2018, subject to the satisfaction of certain milestones for each tranche. Through the end of the drawdown period on October 31, 2018, we had not drawn down from the facility. The Loan Agreement expired on October 31, 2018.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates. Our expenses will also increase as we:

- continue our development of our product candidates, including continuing enrollment in our ongoing Phase 2 clinical trial for AVR-RD-01, the ongoing investigator-sponsored clinical trial of AVR-RD-04 and our ongoing clinical trial of AVR-RD-02;
- initiate additional clinical trials and preclinical studies for our other current and future product candidates;
- seek to identify and develop or in-license or acquire additional product candidates and technologies;
- seek to industrialize our *ex vivo* lentiviral gene therapy approach into a robust, scalable and, if approved, commercially viable process;
- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval;
- hire and retain additional personnel, such as clinical, quality control, commercial and scientific personnel;
- expand our infrastructure, office space and facilities to accommodate our growing employee base, including adding equipment and physical infrastructure to support our research and development; and
- continue to incur additional public company-related costs.

We believe that our existing cash and cash equivalents as of December 31, 2019, together with the estimated net proceeds of $93.5 million from our February 2020 Follow-on Offering, will enable us to fund our operating expenses and capital expenditure requirements into the second quarter of 2022. We have based these estimates on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect. If we receive regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution, depending on where we choose to commercialize.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaboration agreements, government and other third-party funding, strategic alliances, licensing arrangements or marketing and distribution arrangements. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through government and other third-party funding, collaboration agreements, strategic alliances, licensing arrangements or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2019 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods (in thousands):

	Payments Due by Period				
	Total	Less than 1 Year	1 to 3 Years	4 to 5 Years	More than 5 Years
Operating lease commitments (1)	$ 3,055	$ 1,563	$ 1,431	$ 61	$ —
Total	$ 3,055	$ 1,563	$ 1,431	$ 61	$ —

(1) Represents future minimum lease payments under our non-cancelable operating leases for office and laboratory space, which are located in Cambridge, Massachusetts. Those leases will expire from October 2020 to January 2023. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.

We enter into contracts in the normal course of business with CROs, CMOs and other third parties for clinical trials, preclinical research studies and testing and manufacturing services. Payments due upon cancellation consist only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation. These payments are not included in the preceding table as the amount and timing of such payments are not known.

In addition, pursuant to our license agreements with UHN, BioMarin, GenStem and the Lund University rights holders, we are required to make certain milestone and royalty payments to our licensors. See “Business—License Agreements” for additional details regarding our payment obligations to these licensors.

Critical Accounting Policies and Significant Judgments and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States. The preparation of our consolidated financial statements and related disclosures requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenue, costs and expenses, and the disclosure of contingent assets and liabilities in our financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2 to our consolidated financial statements appearing elsewhere in this report, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of these estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- vendors, including central laboratories, in connection with preclinical development activities;
- CROs and investigative sites in connection with preclinical and clinical studies; and
- CMOs in connection with drug substance and drug product formulation of preclinical and clinical trial materials.

We base our expenses related to preclinical studies and clinical trials on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple research institutions and CROs that conduct and manage preclinical studies and clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual or the amount of prepaid expenses accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

Stock-Based Compensation

We measure stock options and other stock-based awards granted to employees and members of our board of directors for their services as directors based on the fair value on the date of the grant and recognize the corresponding compensation expense of those awards over the requisite service period, which is generally the vesting period of the respective award. We have issued stock options, restricted stock and restricted stock units with service-based vesting conditions.

Prior to the adoption of Accounting Standards Update (ASU) No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting (ASU 2018-07)*, as discussed in Note 2 to our consolidated financial statements appearing at the end of this document, the measurement date for non-employee awards was generally the date the services are completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After the adoption of ASU 2018-07, the measurement date for non-employee awards is the later of the adoption date of ASU 2018-07, or the date of grant, without change in the fair value of the award.

We estimate the fair value of each stock option grant using the Black-Scholes option-pricing model, which uses as inputs the estimated fair value of our common stock and assumptions we make for the volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield.

We determined the assumptions for the Black-Scholes option-pricing model as discussed below. Each of these inputs is subjective and generally requires significant judgment to determine.

- *Fair Value of Our Common Stock.* The fair value of our common stock is determined based on the quoted market price of our common stock. Prior to our IPO, our stock was not publicly traded, and therefore we estimated the fair value of our common stock, as discussed in “Determination of the Fair Value of Common Stock” below.
- *Expected Term.* The expected term represents the period that the stock-based awards are expected to be outstanding. The expected term of stock options granted has been determined using the simplified method, which uses the midpoint between the vesting date and the contractual term.
- *Risk-Free Interest Rate.* The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the date of grant for zero-coupon U.S. Treasury constant maturity notes with terms approximately equal to the stock-based award’s expected term.
- *Expected Volatility.* Because we do not have long-term trading history of our common stock, the expected volatility was derived from the average historical stock volatilities of several public companies within our industry that we consider to be comparable to our business over a period equivalent to the expected term of the stock-based awards.
- *Dividend Rate.* The expected dividend is zero as we have not paid and do not anticipate paying any dividends in the foreseeable future.

If any of the assumptions used in the Black-Scholes model change significantly, stock-based compensation for future awards may differ materially compared with the awards granted previously.

Determination of the Fair Value of Common Stock

The fair value of our common stock is determined based on the quoted market price of our common stock.

Prior to our IPO, there was no public market for our common stock, and consequently, the estimated fair value of our common stock was determined by our board of directors as of the date of each option grant, with input from management, considering third-party valuations of our common stock as well as our board of directors’ assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent third-party valuation through the date of the grant. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants’ Accounting and Valuation Guide, Valuation of Privately-Held-Company Equity Securities Issued as Compensation. After a public trading market for our common stock was established following the closing of our IPO, it was no longer necessary for our board of directors to estimate the fair market value of our common stock in connection with our accounting for granted equity awards.

Valuation of Derivative Liability

The fair value of the derivative liability recognized in connection with our stock purchase agreement with UHN was determined based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The fair value of the derivative liability was determined using the probability-weighted expected return method, or PWERM, which considered as inputs the type and probability of occurrence of an IPO dilution event, the amount of the payment, the expected timing of an IPO dilution event and a risk-adjusted discount rate.

Valuation of Warrant Liability

In connection with entering into the Loan Agreement, we agreed to issue a warrant to purchase shares of our Series A preferred stock to the lender. We classified the warrant as a liability on our consolidated balance sheet because the warrant represented a free-standing financial instrument that may have required us to transfer assets upon exercise. The warrant liability was initially recorded at fair value upon the date of the warrant issuance and was subsequently remeasured to fair value at each reporting date. Changes in the fair value of the warrant liability were recognized as a component of other income (expense), net in the consolidated statements of operations.

We utilized the Black-Scholes option-pricing model, which incorporates assumptions and estimates, to value the warrant. We assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions was obtained. Estimates and assumptions impacting the fair value measurement included the fair value per share of the underlying equity instruments issuable upon exercise of the warrant, the remaining contractual term of the warrant, risk-free interest rate, expected dividend yield and expected volatility of the underlying preferred stock. Prior to our IPO in 2018, we had been a private company and lacked company-specific historical and implied volatility information of our stock. Therefore, we estimated expected stock volatility based on the historical volatility of publicly traded peer companies for a term equal to the remaining contractual term of the warrant. The risk-free interest rate was determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the remaining contractual term of the warrant. We estimated a 0% dividend yield based on the fact that we have never paid or declared dividends.

Upon the closing of our IPO, the preferred stock warrant became exercisable for common stock instead of preferred stock. The carrying amount of the warrant to purchase preferred stock as of the date of IPO was transferred to additional paid in capital. No further revaluation was required for the warrant to purchase common stock.

Emerging Growth Company Status

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. We may take advantage of these exemptions until we are no longer an emerging growth company. Section 107 of the JOBS Act provides that an emerging growth company can take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards. We have elected to use the extended transition period for complying with new or revised accounting standards and, as a result of this election, our financial statements may not be comparable to companies that comply with public company effective dates. We may take advantage of these exemptions up until the last day of the fiscal year following the fifth anniversary of our IPO or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company if we have more than $1.07 billion in annual revenue, we have more than $700.0 million in market value of our stock held by non-affiliates (and we have been a public company for at least 12 months and have filed one annual report on Form 10-K) or we issue more than $1.0 billion of non-convertible debt securities over a three-year period.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the Securities and Exchange Commission.

Recently Issued Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 2 to our audited financial statements appearing elsewhere in this report.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

Interest Rate Risk

As of December 31, 2019, we had cash and cash equivalents of $187.0 million, which consisted of cash and money market funds. Interest income is sensitive to changes in the general level of interest rates; however, due to the nature of these investments, an immediate 10% change in interest rates would not have a material impact on our cash and cash equivalents, financial position or results of operations.

Foreign Currency Exchange Risk

We are exposed to foreign exchange rate risk. Our headquarters are located in the United States, where the majority of our general and administrative expenses and research and development costs are incurred in U.S. dollars. A portion of our research and development costs are incurred by our subsidiaries in Australia and Canada, whose functional currencies are the U.S. dollar but engage in transactions in Australian dollars and Canadian dollars, respectively. During each of the years ended December 31, 2019 and 2018, we recognized immaterial foreign currency transaction losses. These losses primarily related to unrealized and realized foreign currency gains and losses as a result of transactions entered into by our Australian and Canadian subsidiaries in currencies other than the U.S. dollar. These foreign currency transaction gains and losses were recorded in other expense, net in our consolidated statements of operations. We believe that a 10% change in the exchange rate between the U.S. dollar, Australian dollar and Canadian dollar would not have a material impact on our financial position or results of operations.

As we continue to grow our business, our results of operations and cash flows will be subject to fluctuations due to changes in foreign currency exchange rates, which could adversely impact our results of operations. To date, we have not entered into any foreign currency hedging contracts to mitigate our exposure to foreign currency exchange risk.

Item 8. Financial Statements and Supplementary Data

All financial statements and supplementary data required to be filed hereunder are filed as listed under Item 15(a) of this Annual Report on Form 10-K and are incorporated herein by this reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer (our principal executive officer and principal financial officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2019. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2019, our Chief Executive Officer and Chief Financial Officer concluded that, as a result of the material weaknesses in our internal control over financial reporting as described below under “Management’s Report on Internal Control Over Financial Reporting” and in Part II, Item 1A. of this report, our disclosure controls and procedures were not effective as of December 31, 2019. Notwithstanding the material weaknesses, our management has concluded that the financial statements included elsewhere in this report present fairly, in all material respects, our financial position, results of operations and cash flows in conformity with GAAP.

Management's Annual Report on Internal Control over Financial Reporting

In our Annual Report on Form 10-K for the year ended December 31, 2018, we reported material weaknesses in our internal control over financial reporting related to deficiencies in our controls over the financial statement close process, including over complex accounting issues, expense classification and accrued research and development expenses, as well as the cash disbursement process. During 2019, we took a number of actions, including the efforts outlined below, designed to improve our internal control over financial reporting to remediate these material weaknesses. These efforts include:

- hiring additional qualified accounting and financial planning and analysis personnel, including an Assistant Controller and Senior Director of Financial Planning and Analysis;
- conducting a review of our IT infrastructure, personnel and services, and hiring a Senior Director of Information Technology;
- engaging a professional accounting services firm to help us assess and commence documentation of our internal controls for complying with the Sarbanes-Oxley Act of 2002;
- strengthening, formalizing, documenting and testing accounting processes and internal controls;
- engaging consultants to provide additional technical accounting expertise; and
- implementing new financial software systems including a purchase requisition system, expense reporting system and a system to track and account for stock-based awards to automate these processes.

We believe significant progress was made in 2019 to enhance and strengthen our internal control over financial reporting. However, while we believe our internal controls were properly designed and implemented as of December 31, 2019, they were not in all cases in place for a sufficient period of time to demonstrate operating effectiveness as of December 31, 2019. As a result, management has concluded that the material weaknesses were not fully remediated as of December 31, 2019.

The measures we are implementing are subject to continued management review supported by confirmation and testing, as well as audit committee oversight. Management remains committed to remediating these material weaknesses. We will continue to implement measures to remedy our internal control deficiencies, though there can be no assurance that our efforts will be successful or avoid potential future material weaknesses.

Changes in Internal Control over Financial Reporting

Other than the changes intended to remediate the material weaknesses noted above, no change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the quarter ended December 31, 2019 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

PART III

Certain information required by Part III is omitted from this Annual Report on Form 10-K and is incorporated by reference from our definitive proxy statement relating to our 2020 annual meeting of stockholders, pursuant to Regulation 14A of the Securities Exchange Act of 1934, as amended, also referred to in this Annual Report on Form 10-K as our 2020 Proxy Statement, which we expect to file with the SEC no later than April 29, 2020.

Item 10. Directors, Executive Officers and Corporate Governance

Information required by this item with respect to our directors and executive officers and compliance with Section 16(a) of the Exchange Act will be included in our 2020 Proxy Statement and is incorporated herein by reference.

Item 11. Executive Compensation

The information required by this item regarding executive compensation will be included in our 2020 Proxy Statement and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item regarding security ownership of certain beneficial owners and management and securities authorized for issuance under equity compensation plans will be included in our 2020 Proxy Statement and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item regarding certain relationships and related transactions and director independence will be included in our 2020 Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The information required by this item regarding principal accounting fees and services will be included in our 2020 Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) The following documents are included in this Annual Report on Form 10-K:

1. The following Report and Consolidated Financial Statements of the Company are included in this Annual Report:

   Report of Independent Registered Public Accounting Firm

   Consolidated Balance Sheets

   Consolidated Statements of Operations and Comprehensive Loss

   Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' (Deficit) Equity

   Consolidated Statements of Cash Flows

   Notes to Consolidated Financial Statements

2. All financial schedules have been omitted because the required information is either presented in the consolidated financial statements or the notes thereto or is not applicable or required.

3. The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the signature page of this Annual Report on Form 10-K. The exhibits listed in the Exhibit Index are incorporated by reference herein.

Item 16. Form 10-K Summary

Not Applicable.

AVROBIO, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of AVROBIO, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of AVROBIO, Inc. (the Company) as of December 31, 2019 and 2018, the related consolidated statements of operations and comprehensive loss, redeemable convertible preferred stock and stockholders' (deficit) equity and cash flows for each of the years then ended, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2019 and 2018, and the results of its operations and its cash flows for each of the years then ended, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2018.
Boston, Massachusetts
March 16, 2020

AVROBIO, INC.
CONSOLIDATED BALANCE SHEETS
(amounts in thousands, except share and per share data)

	December 31, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 187,043	$ 126,302
Prepaid expenses and other current assets	8,658	3,718
Total current assets	195,701	130,020
Property and equipment, net	3,696	2,634
Other assets	1,117	825
Total assets	$ 200,514	$ 133,479
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 3,949	$ 2,784
Accrued expenses and other current liabilities	10,068	7,822
Total current liabilities	14,017	10,606
Deferred rent, net of current portion	484	689
Total liabilities	14,501	11,295
Commitments and contingencies (Note 14)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 10,000,000 shares authorized and no shares issued or outstanding as of December 31, 2019 and 2018		—
Common stock, $0.0001 par value; 150,000,000 shares authorized as of December 31, 2019 and 2018; 31,673,058 and 23,959,903 shares issued as of December 31, 2019 and 2018, respectively; 31,642,806 and 23,806,628 shares outstanding as of December 31, 2019 and 2018, respectively	3	2
Additional paid-in capital	330,714	193,921
Accumulated deficit	(144,704)	(71,739)
Total stockholders' equity	186,013	122,184
Total liabilities and stockholders' equity	$ 200,514	$ 133,479

The accompanying notes are an integral part of these consolidated financial statements.

AVROBIO, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(amounts in thousands, except share and per share data)

	Year Ended December 31, 2019	Year Ended December 31, 2018
Operating expenses:		
Research and development	$ 54,974	$ 35,095
General and administrative	20,835	11,148
Total operating expenses	75,809	46,243
Loss from operations	(75,809)	(46,243)
Other income (expense):		
Interest income	2,934	1,726
Change in fair value of preferred stock warrant liability	—	(162)
Change in fair value of derivative liability	—	(1,629)
Other expense	(90)	(53)
Total other income (expense), net	2,844	(118)
Net loss	$ (72,965)	$ (46,361)
Comprehensive loss	$ (72,965)	$ (46,361)
Reconciliation of net loss to net loss attributable to common stockholders:		
Net loss	$ (72,965)	$ (46,361)
Accretion of issuance costs on redeemable convertible preferred stock	—	(2,243)
Net loss attributable to common stockholders—basic and diluted	$ (72,965)	$ (48,604)
Net loss per share attributable to common stockholders—basic and diluted (Note 13)	$ (2.66)	$ (3.62)
Weighted-average number of common shares used in computing net loss per share attributable to common stockholders—basic and diluted	27,432,489	13,435,478

The accompanying notes are an integral part of these consolidated financial statements.

AVROBIO, INC.
CONSOLIDATED STATEMENTS OF REDEEMABLE CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS’ (DEFICIT) EQUITY
(amounts in thousands, except share data)

	Series Seed Redeemable Convertible Preferred Stock		Series A Redeemable Convertible Preferred Stock		Series B Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Deficit	Total Stockholders’ (Deficit) Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount			
Balance as of December 31, 2017	3,333,333	$ 1,500	31,450,499	$ 25,000	—	$ —	2,305,173	$ —	$ 339	$ (23,474)	$ (23,135)
Issuance of series B redeemable convertible preferred stock, net of issuance costs of $2,243	—	—	—	—	28,285,557	58,257	—	—	—	—	—
Issuance of series B redeemable convertible preferred stock to settle accrued liability of license cost	—	—	—	—	233,765	500	—	—	—	—	—
Accretion of issuance costs related to redeemable convertible preferred stock	—	—	—	—	—	2,243	—	—	(339)	(1,904)	(2,243)
Issuance of common stock upon IPO, net of issuance costs of $2,628	—	—	—	—	—	—	6,035,151	1	104,012	—	104,013
Stock-based compensation expense	—	—	—	—	—	—	—	—	2,196	—	2,196
Reclassification of warrants to purchase redeemable convertible stock into warrants to purchase common stock	—	—	—	—	—	—	—	—	197	—	197
Conversion of redeemable convertible preferred stock into common stock	(3,333,333)	(1,500)	(31,450,499)	(25,000)	(28,519,322)	(61,000)	15,320,213	1	87,499	—	87,500
Exercise of warrants to purchase common stock	—	—	—	—	—	—	6,091	—	—	—	—
Vesting of restricted stock awards	—	—	—	—	—	—	123,026	—	—	—	—
Exercise of stock options	—	—	—	—	—	—	16,974	—	17	—	17
Net loss	—	—	—	—	—	—	—	—	—	(46,361)	(46,361)
Balance as of December 31, 2018	—	—	—	—	—	—	23,806,628	2	193,921	(71,739)	122,184
Vesting of restricted stock awards	—	—	—	—	—	—	123,024	—	—	—	—
Exercise of stock options	—	—	—	—	—	—	236,483	—	502	—	502
Issuance of common stock upon public offering, net of offering costs of $525	—	—	—	—	—	—	7,475,000	1	129,464	—	129,465
Issuance of common stock under 2018 employee stock purchase plan							1,671		27		27
Stock-based compensation expense									6,800		6,800
Net loss	—	—	—	—	—	—	—	—	—	(72,965)	(72,965)
Balance as of December 31, 2019	—	$ —	—	$ —	—	$ —	31,642,806	$ 3	$ 330,714	$ (144,704)	$ 186,013

The accompanying notes are an integral part of these consolidated financial statements.

AVROBIO, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(amounts in thousands)

	Year Ended December 31,	
	2019	2018
Cash flows from operating activities:		
Net loss	$ (72,965)	$ (46,361)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	6,800	2,196
Depreciation and amortization expense	850	380
Amortization of deferred offering costs	—	37
Impairment loss of property and equipment	—	235
Deferred rent expense	(172)	(105)
Change in fair value of preferred stock warrant liability	—	162
Change in fair value of derivative liability	—	1,629
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(4,888)	(3,037)
Other assets	(241)	(115)
Accounts payable	1,028	2,018
Accrued expenses and other current liabilities	1,920	5,313
Net cash used in operating activities	(67,668)	(37,648)
Cash flows from investing activities:		
Purchases of property and equipment	(1,585)	(1,832)
Net cash used in investing activities	(1,585)	(1,832)
Cash flows from financing activities:		
Proceeds from issuance of redeemable convertible preferred stock, net of issuance costs	—	58,257
Proceeds from issuance of common shares upon completion of public offering, net of offering costs	129,465	104,013
Payment of dilution liability	—	(2,000)
Exercise of stock options	502	17
Proceeds from the issuance of shares under the employee stock purchase plan	27	—
Net cash provided by financing activities	129,994	160,287
Net increase in cash, cash equivalents and restricted cash	60,741	120,807
Cash, cash equivalents and restricted cash at beginning of period	126,794	5,987
Cash, cash equivalents and restricted cash at end of period	$ 187,535	$ 126,794
Supplemental disclosure of non-cash investing and financing activities:		
Purchases of property and equipment included in accounts payable and accrued expenses	$ 582	$ 256
Property and equipment held for sale	$ —	$ 19
Deferred offering costs included in accrued expenses and accounts payable	$ 104	$ —
Purchase of property and equipment paid for by landlord	$ —	$ 842
Accretion of issuance costs related to redeemable convertible preferred stock	$ —	$ 2,243

The accompanying notes are an integral part of these consolidated financial statements.

1. Nature of the Business

AVROBIO, Inc. (the "Company" or "AVROBIO") is a clinical-stage gene therapy company focused on developing potentially curative *ex vivo* lentiviral gene therapies to treat rare diseases following a single dose treatment regimen.

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including but not limited to, risks associated with completing preclinical studies and clinical trials, receiving regulatory approvals for product candidates, development by competitors of new biopharmaceutical products, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize revenue from product sales.

Through December 31, 2019, the Company has funded its operations primarily with proceeds from the sale of Seed redeemable convertible preferred stock (the "Series Seed Preferred Stock"), series A redeemable convertible preferred stock (the "Series A Preferred Stock") and series B redeemable convertible preferred stock (the "Series B Preferred Stock"), (the Series Seed Preferred Stock, the Series A Preferred Stock and the Series B Preferred Stock are collectively referred to as the "Preferred Stock") and common stock through the Company's initial public offering ("IPO"). The Company has incurred recurring losses since its inception, including net losses of $72,965 and $46,361 for the years ended December 31, 2019 and 2018, respectively. In addition, as of December 31, 2019, the Company had an accumulated deficit of $144,704. Although the Company has incurred recurring losses and expects to continue to incur losses for the foreseeable future, the Company expects that its existing cash and cash equivalents on hand as of December 31, 2019 of $187,043, together with net proceeds from the follow on public offering completed in February 2020 ("the February 2020 Follow-On Offering") (see Note 17) will be sufficient to fund current planned operations and capital expenditure requirements for at least the next twelve months from the filing date of this Annual Report on Form 10-K with the SEC. However, the future viability of the Company is dependent on its ability to raise additional capital to finance its operations. The Company's inability to raise capital as and when needed could have a negative impact on its financial condition and ability to pursue its business strategies. There can be no assurance that the current operating plan will be achieved or that additional funding will be available on terms acceptable to the Company, or at all.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of AVROBIO, Inc. and its wholly owned subsidiaries. All intercompany transactions and balances have been eliminated in consolidation.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual for research and development expenses, stock-based compensation expense, the valuation of equity and derivative instruments and the recoverability of the Company's net deferred tax assets and related valuation allowance. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

(amounts in thousands, except share and per share data)

Cash and Cash Equivalents

The Company considers all highly liquid investments purchased with original maturities of 90 days or less at acquisition to be cash equivalents. Cash and cash equivalents include cash held in banks and amounts held in interest-bearing money market accounts. Cash equivalents are carried at cost, which approximates their fair market value.

Restricted Cash

As of both December 31, 2019 and 2018, restricted cash consisted of $492 used to secure the letters of credit for the benefit of the landlord in connection with the Company's lease agreements (Note 14). These amounts are classified as other assets in the Company's consolidated balance sheets.

Concentrations of Credit Risk

The Company has no significant off-balance sheet risk, such as foreign exchange contracts, option contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and restricted cash. Periodically, the Company maintains deposits in accredited financial institutions in excess of federally insured limits. The Company deposits its cash and cash equivalents in financial institutions that it believes have high credit quality and has not experienced any losses on such accounts and does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

Deferred Issuance Costs

The Company capitalizes certain legal, professional accounting and other third-party fees that are directly associated with in-process equity financings as deferred issuance costs until such financings are consummated. After consummation of the equity financing, these costs are recorded as a reduction of the proceeds generated as a result of the offering. Should the planned equity financing be abandoned, the deferred issuance costs will be expensed immediately as a charge to operating expenses in the consolidated statements of operations. As of December 31, 2019, the Company recorded deferred issuance costs of $133 within other assets on the consolidated balance sheet related to a follow-on offering of common stock completed in February 2020. There were no amounts deferred as of December 31, 2018.

Property and Equipment

Property and equipment are recorded at cost. Depreciation and amortization is calculated using the straight-line method over the following estimated useful lives of the assets:

	Estimated Useful Life
Laboratory and office equipment	5 years
Computer equipment and software	2 years
Leasehold improvements	Lesser of lease term or 10 years

Upon disposal, retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is included in the results of operations. Expenditures for repairs and maintenance that do not improve or extend the lives of the respective assets are charged to expense as incurred.

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, determined based on discounted cash flows. During the year ended December 31, 2018, the Company recorded an impairment loss of $235 on long-lived assets related to leasehold improvements. The Company did not record any impairment loss during the year ended December 31, 2019.

Fair Value Measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP (see Note 3). Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

The carrying amounts of the Company's financial instruments, which include cash and cash equivalents, restricted cash, accounts payable, and accrued expenses, approximated their fair values at December 31, 2019 and 2018 due to the short-term nature of these instruments.

The Company has evaluated the estimated fair value of financial instruments using available market information. The use of different market assumptions, estimation methodologies, or both, could have a significant effect on the estimated fair value amounts. See Note 3 for further discussion.

Segment Information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker, or decision-making group, in making decisions on how to allocate resources and assess performance. The Company's chief operating decision maker is the chief executive officer ("CEO"). The Company and the CEO view the Company's operations and manage its business as one operating segment. All material long-lived assets of the Company reside in the United States.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries, stock-based compensation and benefits, facilities costs, depreciation, third-party license fees, and external costs of outside vendors engaged to conduct preclinical development activities and clinical trials as well as to manufacture research and development materials. Non-refundable prepayments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized. Such amounts are recognized as an expense as the goods are delivered or the related services are performed or until it is no longer expected that the goods will be delivered or the services rendered.

The Company has entered into various research and development related contracts with parties both inside and outside of the United States. The payments related to these agreements are recorded as research and development expenses as incurred. The Company records accrued liabilities for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Stock-Based Compensation

For stock-based awards issued to employees and members of the Company's board of directors (the "Board") for their services on the Board, the Company measures the estimated fair value of the stock-based award on the date of grant and recognizes compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award. The Company issues stock-based awards with only service-based vesting conditions and records the expense for these awards using the straight-line method. The Company has not issued any stock-based awards with performance- or market-based vesting conditions. The Company accounts for forfeitures as they occur.

Prior to the adoption of Accounting Standards Update ("ASU") No. 2018-07, *Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting*, the measurement date for non-employee awards was generally the date the services are completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After adoption of ASU 2018-07, the measurement date for non-employee awards is the later of the adoption date of ASU 2018-07, or the date of grant, without change in the fair value of the award. For stock-based awards granted to nonemployees subject to graded vesting that only contain service conditions, the Company has elected to recognize stock-based compensation expense using the straight-line recognition method.

The Company classifies stock-based compensation expense in its consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's cash compensation costs are classified.

Given the absence of an active market for the Company's common stock prior to the IPO, the Company and the Board, the members of which the Company believes have extensive business, finance, and venture capital experience, were required to estimate the fair value of the Company's common stock at the time of each grant of a stock-based award. The Company and the Board determined the estimated fair value of the Company's equity instruments based on a number of factors, including external market conditions affecting the biotechnology industry sector. The Company and the Board utilized various valuation methodologies in accordance with the framework of the American Institute of Certified Public Accountants' Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its common stock. Each valuation methodology includes estimates and assumptions that require the Company's judgment. These estimates and assumptions include a number of objective and subjective factors in determining the value of the Company's common stock at each grant date, including: (1) prices paid for the Company's redeemable convertible preferred stock, which the Company had sold to outside investors in arm's-length transactions, and the rights, preferences, and privileges of the Company's redeemable convertible preferred stock and common stock; (2) valuations performed by an independent valuation specialist; (3) the Company's stage of development; (4) the fact that the grants of stock-based awards involved illiquid securities in a private company; and (5) the likelihood of achieving a liquidity event for the common stock underlying the stock-based awards, such as an IPO or sale of the Company, given prevailing market conditions.

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option pricing model. As there was no public market for its common stock prior to June 21, 2018, which was the first day of trading, and as the trading history of the Company's common stock was limited through December 31, 2019, the Company determined the volatility for awards granted based on an analysis of reported data for a group of guideline companies that issued options with substantially similar terms. The expected volatility has been determined using a weighted-average of the historical volatility measures of this group of guideline companies. The Company expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded stock price. The expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. The Company has not paid, and does not anticipate paying, cash dividends on its common stock; therefore, the expected dividend yield is assumed to be zero.

See Note 10 for the assumptions used by the Company in determining the grant date fair value of stock-based awards granted, as well as a summary of the stock-based award activity under the Company's stock-based compensation plan for the year ended December 31, 2019.

Warrant to Purchase Preferred Stock

Prior to the IPO, the Company classified the warrant for the purchase of shares of its redeemable convertible preferred stock (see Note 7) as a liability on its consolidated balance sheets as the warrant was a free-standing financial instrument that may require the Company to transfer assets upon exercise. The preferred stock warrant liability was initially recorded at fair value upon the date of issuance and was subsequently remeasured to fair value at each reporting date. Changes in the fair value of the warrant to purchase preferred stock were recognized as a component of other income (expense), net in the consolidated statements of operations and comprehensive loss.

The Company utilized the Black-Scholes option-pricing model, which incorporates assumptions and estimates, to value the warrant. The Company assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions was obtained. Estimates and assumptions impacting the fair value measurement included the fair value per share of the underlying redeemable convertible preferred stock issuable upon exercise of the warrant, the remaining contractual term of the warrant, the risk-free interest rate, the expected dividend yield and the expected volatility of the price of the underlying redeemable convertible preferred stock.

Upon the IPO, the warrant to purchase preferred stock was converted to a warrant to purchase common stock. The carrying amount of the warrant to purchase preferred stock as of the date of IPO was transferred to the account of additional paid in capital. No further revaluation was needed for the warrant to purchase common stock.

Comprehensive Income (Loss)

Comprehensive income (loss) is defined as the change in stockholders' equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Comprehensive income (loss) includes net income (loss) as well as other changes in stockholders' (deficit) equity which includes certain changes in equity that are excluded from net income (loss). Comprehensive loss has been disclosed in the accompanying statements of operations and comprehensive loss and equals the Company's net loss for all periods presented.

Foreign Currency Translation

The functional currency of the Company's international operations in Canada and Australia is the U.S. dollar. Accordingly, all operating assets and liabilities of these international subsidiaries are remeasured into U.S. dollars using the exchange rates in effect at the balance sheet date or historical rates, as appropriate, while expenses are remeasured into U.S. dollars at the average rates in effect during the period. Any differences resulting from the remeasurement of assets, liabilities, and operations of the Canadian and Australian subsidiaries are recorded within other income (expense), net in the consolidated statements of operations and comprehensive loss. During the years ended December 31, 2019 and 2018, the Company recorded foreign exchange losses of $90 and $51, respectively, in other expense.

Income Taxes

Deferred tax assets and liabilities are determined on the basis of the differences between the consolidated financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established.

The Company accounts for uncertain tax positions recognized in the consolidated financial statements by prescribing a more-likely-than-not threshold for financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate as well as the related net interest and penalties.

Leases

The Company categorizes leases at their inception as either operating or capital leases. On certain lease arrangements, the Company may receive rent holidays or other incentives. The Company recognizes lease costs on a straight-line basis once control of the space is achieved, without regard to deferred payment terms, such as rent holidays, that defer the commencement date of required payments or escalating payment amounts. The difference between required lease payments and rent expense has been recorded as deferred rent and other accrued expenses and other current liabilities in the accompanying consolidated balance sheets. Additionally, incentives received are treated as a reduction of costs over the term of the agreement, as they are considered an inseparable part of the lease agreement.

Net Income (Loss) per Share Attributable to Common Stockholders

Net income (loss) per share attributable to common stockholders is determined using the two-class method, which includes the weighted-average number of shares of common stock outstanding during the period and other securities that participate in dividends (a participating security). In periods of income, the redeemable convertible preferred stock would be considered participating securities because the shares include rights to participate in dividends with the common stock; however, the redeemable convertible preferred stock is not considered a participating security in periods of loss as they do not have an obligation to share in the Company's net losses.

Under the two-class method, basic net income (loss) per share attributable to common stockholders is computed by dividing the net income (loss) attributable to common stockholders by the weighted-average number of shares of common stock outstanding during the period. Diluted net income (loss) per share attributable to common stockholders is computed using the more dilutive of (1) the two-class method or (2) the if-converted method. The Company allocates net income first to the holders of Preferred Stock based on dividend rights under the Company's certificate of incorporation and then to preferred and common stockholders based on ownership interests.

Subsequent Event Considerations

The Company considers events or transactions that occur after the balance sheet date but prior to the issuance of the consolidated financial statements to provide additional evidence for certain estimates or to identify matters that require additional disclosure. Subsequent events have been evaluated as required. The Company has evaluated all subsequent events and determined that there are no material recognized or unrecognized subsequent events requiring disclosure, other than as disclosed in these notes to the consolidated financial statements. See Note 17 for further information.

Emerging Growth Company Status

The Company is an "emerging growth company," as defined in the Jumpstart Our Business Startups Act, or JOBS Act, and may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. The Company may take advantage of these exemptions until the Company is no longer an "emerging growth company." Section 107 of the JOBS Act provides that an "emerging growth company" can take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards. The Company has elected to use the extended transition period for complying with new or revised accounting standards and as a result of this election, its consolidated financial statements may not be comparable to companies that comply with public company effective dates. The Company may take advantage of these exemptions up until the last day of the fiscal year following the fifth anniversary of an offering or such earlier time that it is no longer an "emerging growth company."

Recently Adopted Accounting Pronouncements

In June 2018, the FASB issued ASU No. 2018-07, *Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07"). ASU 2018-07 amends the FASB Accounting Standards Codification ("ASC") to expand the scope of FASB ASC Topic 718, *Compensation-Stock Compensation*, to include accounting for share-based payment transactions for acquiring goods and services from non-employees. The amendments in ASU 2018-07 are effective for all entities for annual periods, and interim periods within those annual periods, beginning after December 15, 2018. Early adoption is permitted. The Company early adopted this guidance at the beginning of the fourth quarter of 2018. There was no material impact on the consolidated financial statements as a result of this adoption.

(amounts in thousands, except share and per share data)

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers (Topic 606)* (“ASU 2014-09”), which supersedes existing revenue recognition guidance under GAAP. The standard’s core principle is that a company will recognize revenue when it transfers promised goods or services to customers in an amount that reflects the consideration to which the company expects to be entitled in exchange for those goods or services. The standard defines a five-step process to achieve this principle and will require companies to use more judgment and make more estimates than under the current guidance. The Company expects that these judgments and estimates will include identifying performance obligations in the customer contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each separate performance obligation. ASU 2014-09 also requires additional disclosure about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts. The Company early adopted ASU 2014-09 at the beginning of the fourth quarter of 2018. The adoption of ASU 2014-09 did not have an impact on the Company’s consolidated financial statements as the Company does not currently have any revenue-generating arrangements.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation—Stock Compensation (Topic 718): Scope of Modification Accounting* (“ASU 2017-09”), which clarifies when to account for a change to the terms or conditions of a share-based payment award as a modification. Under the new guidance, modification accounting is required only if the fair value, the vesting conditions, or the classification of the award (as equity or liability) changes as a result of the change in terms or conditions. The standard is effective for annual periods beginning after December 15, 2017. Early adoption is permitted, including adoption in any interim period, for (1) public business entities for reporting periods for which financial statements have not yet been issued and (2) all other entities for reporting periods for which financial statements have not yet been made available for issuance. The Company adopted this guidance at the beginning of the fourth quarter of 2018. There was no material impact on the consolidated financial statements as a result of this adoption.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230) Restricted Cash* (“ASU 2016-18”), which requires that a statement of cash flows explain the change during the period in the total of cash, cash equivalents and restricted cash. Therefore, amounts described as restricted cash should be included with cash and cash equivalents when reconciling the beginning of period and end of period amounts shown on the statement of cash flows. The Company early adopted this guidance at the beginning of the fourth quarter of 2018. ASU 2016-18 is effective on a retrospective basis. The cash, cash equivalents and restricted cash balances as of December 31, 2019 and 2018, which are presented in the Company’s consolidated statements of cash flows subsequent to the adoption of ASU 2016-18, consisted of the following:

	December 31, 2019	December 31, 2018
Cash and cash equivalents	$ 187,043	$ 126,302
Other assets	492	492
Cash, cash equivalents and restricted cash	$ 187,535	$ 126,794

Recently Issued Accounting Pronouncements

In December 2019, the FASB issued ASU No. 2019-12, *Simplifying the Accounting for Income Taxes*, or ASU 2019-12. ASU 2019-12 eliminates certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. It also clarifies and simplifies other aspects of the accounting for income taxes. The guidance is effective for fiscal years beginning after December 15, 2020, and interim periods within those fiscal years, with early adoption permitted. The Company is currently evaluating the impact that the adoption of ASU 2019-12 will have on its consolidated financial statements.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework—Changes to the Disclosure Requirements for Fair Value Measurement*, or ASU 2018-13. The amendments in ASU 2018-13 eliminate, add, and modify certain disclosure requirements for fair value measurements. The amendments are effective for interim and annual reporting periods beginning after December 15, 2019, with early adoption permitted for either the entire ASU or only the provisions that eliminate or modify requirements. The amendments with respect to changes in unrealized gains and losses, the range and weighted-average of significant unobservable inputs used to develop Level 3 fair value measurements, and the narrative description of measurement uncertainty are to be applied prospectively. All other amendments are to be applied retrospectively to all periods presented. The Company is currently evaluating the effects the adoption of ASU 2018-13 will have on its disclosures.

In August 2018, the FASB issued ASU No. 2018-15, Intangible-Goodwill and Other Internal-Use Software (Subtopic 350-40) (“ASU 2018-15”). ASU 2018-15 updates guidance regarding accounting for implementation costs associated with a cloud computing arrangement that is a service contract. The amendments under ASU 2018-15 are effective for interim and annual fiscal periods beginning after December 15, 2019, with early adoption permitted. The Company does not expect the adoption of ASU 2018-15 to have a material impact on its consolidated financial statements.

(amounts in thousands, except share and per share data)

In November 2018, the FASB issued ASU No. 2018-18, Collaborative Arrangements (Topic 808)—Clarifying the Interaction between Topic 808 and Topic 606 ("ASU 2018-18"). The amendments in ASU 2018-18 clarify that certain transactions between collaborative arrangement participants should be accounted for as revenue under ASC 606 when the collaborative arrangement participant is a customer in the context of a unit of account. The amendments under ASU 2018-18 are effective for interim and annual fiscal periods beginning after December 15, 2019, with early adoption permitted. The amendments in ASU 2018-18 should be applied retrospectively to the date of initial application of ASC 606. The Company does not expect the adoption of ASU 2018-18 to have a material impact on its consolidated financial statements.

In June 2016, the FASB issued ASU No. 2016-13, Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments ("ASU 2016-13"). ASU 2016-13 requires that credit losses be reported as an allowance using an expected losses model, representing the entity's current estimate of credit losses expected to be incurred. The accounting guidance currently in effect is based on an incurred loss model. For available-for-sale debt securities with unrealized losses, this standard now requires allowances to be recorded instead of reducing the amortized cost of the investment. The amendments under ASU 2016-13 are effective for interim and annual fiscal periods beginning after December 15, 2019. The Company does not expect the adoption of ASC 2016-13 to have a material impact on its consolidated financial statements.

In February 2016, the FASB issued ASU No. 2016-02, (Topic 842) Leases ("ASU 2016-02"). ASU 2016-02 requires an entity to recognize assets and liabilities arising from a lease for both financing and operating leases. The ASU will also require new qualitative and quantitative disclosures to help investors and other financial statement users better understand the amount, timing, and uncertainty of cash flows arising from leases. For public entities, ASU 2016-02 is effective for fiscal years beginning after December 15, 2018. As a result of the Company having elected the extended transition period for complying with new or revised accounting standards pursuant to Section 107(b) of the JOBS Act, ASU 2016-02 is effective for the Company for the year ended December 31, 2021, and all interim periods thereafter. Early adoption is permitted. The Company is currently evaluating the impact that the adoption of ASU 2016-02 will have on its consolidated financial statements.

3. Fair Value of Financial Assets and Liabilities

The following table presents information about the Company's financial assets and liabilities measured at fair value on a recurring basis and indicates the level of the fair value hierarchy utilized to determine such fair values as of December 31, 2019 and 2018:

	Fair Value Measurements as of December 31, 2019 Using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	$ 186,797	$ —	$ —	$ 186,797
Restricted cash	492	—	—	492
	$ 187,289	$ —	$ —	$ 187,289

	Fair Value Measurements as of December 31, 2018 Using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	$ 126,047	$ —	$ —	$ 126,047
Restricted cash	492	—	—	492
	$ 126,539	$ —	$ —	$ 126,539

During the years ended December 31, 2019 and 2018, there were no transfers between Level 1, Level 2 and Level 3.

(amounts in thousands, except share and per share data)

Valuation of the Warrant to Purchase Preferred Stock

In connection with a loan and security agreement in 2017 (the "Loan Agreement") (Note 7), the Company agreed to issue a warrant to the lender for the purchase shares of Series A Preferred Stock. The fair value of the warrant to purchase preferred stock was determined based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy.

In order to determine the fair value of the warrant to purchase preferred stock, the Company utilized available facts and circumstances to estimate the number of shares of Series A Preferred Stock for which the warrant would ultimately be exercisable. The Company then used the Black-Scholes option-pricing model, which incorporates assumptions and estimates, to value the warrant to purchase preferred stock. Estimates and assumptions impacting the fair value measurement included the fair value of the underlying shares of Series A Preferred Stock, the remaining contractual term of the warrant, risk-free interest rate, expected dividend yield and expected volatility of the price of the underlying preferred stock. The Company determined the fair value of the underlying preferred stock based on various valuation methodologies. The Company lacks company-specific historical and implied volatility information of its stock. Therefore, it estimated its expected stock volatility based on the historical volatility of publicly traded guideline companies for a term equal to the remaining contractual term of the warrant. The risk-free interest rate was determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the remaining contractual term of the warrant. The Company estimated no expected dividend yield based on the fact that the Company has never paid or declared dividends and does not intend to do so in the foreseeable future. Upon the IPO, the warrant to purchase preferred stock was converted to a warrant to purchase common stock. The carrying amount of warrant to purchase preferred stock as of the date of IPO was transferred to the account of additional paid in capital.

The following table sets forth a summary of changes in the fair value of the Company's preferred stock warrant liability for which fair value was determined by Level 3 inputs:

	Warrant Liability
Balance as of December 31, 2017	$ 35
Change in fair value	162
Conversion of preferred stock warrant to common stock warrant	(197)
Balance as of December 31, 2018	$ —

Valuation of Derivative

In January 2016, in connection with a license agreement entered into with University Health Network ("UHN"), and as part of the initial consideration for the license, the Company issued 1,161,665 shares of common stock to UHN pursuant to a stock purchase agreement (the "Stock Purchase Agreement"). The Stock Purchase Agreement contained a provision requiring the Company to make a cash payment to UHN of up to $2,000 if UHN's fully diluted ownership is reduced within specified percentages as part of an initial public offering by the Company. The Company concluded the anti-dilution feature represented a derivative instrument and should be measured at fair value, with changes in fair value recognized as a gain or loss to other income (expense), net in the consolidated statements of operations and comprehensive loss.

On June 21, 2018, in connection with the Company's IPO, the Company remeasured the fair value of the derivative to $2,000 as the Company was required to pay the dilution payment as mentioned above, which the Company paid in July 2018. An increase in fair value of $1,629 was recorded in other expense in the accompanying consolidated statement of operations and comprehensive loss for the year ended December 31, 2018.

(amounts in thousands, except share and per share data)

The following table sets forth a summary of changes in the fair value of the Company's derivative liability for which fair value is determined by Level 3 inputs:

	Derivative Liability
Balance as of December 31, 2017	$ 371
Change in fair value	1,629
Payment	(2,000)
Balance as of December 31, 2018	$ —

4. Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following:

	December 31, 2019	December 31, 2018
Tax incentive refund	$ 1,916	$ 1,325
Prepaid research and development costs	4,915	981
Prepaid insurance	897	316
Interest income receivable	224	220
Prepaid rent	86	81
Other current assets	620	795
	$ 8,658	$ 3,718

5. Property and Equipment, Net

Property and equipment, net consisted of the following:

	December 31, 2019	December 31, 2018
Laboratory and office equipment	$ 3,456	$ 1,624
Leasehold improvements	1,340	1,260
Computer equipment and software	134	134
	4,930	3,018
Less: Accumulated depreciation and amortization	(1,234)	(384)
	$ 3,696	$ 2,634

Depreciation and amortization expense for the years ended December 31, 2019 and 2018 was $850 and $380, respectively.

6. Accrued Expenses

Accrued expenses consisted of the following:

	December 31, 2019	December 31, 2018
Compensation and benefit costs	$ 3,028	$ 2,616
Research and development costs	5,794	3,969
Consulting and professional fees	917	320
Other liabilities	329	917
	$ 10,068	$ 7,822

7. Loan Agreement and Warrant to Purchase Preferred Stock

On June 23, 2017, the Company entered into the Loan Agreement with a lender, which provided for the issuance of term loans of up to $10,000, subject to the achievement of various development and corporate milestones. Any outstanding principal amounts under the Loan Agreement accrued interest at a floating per annum rate equal to the greater of 1% and the “prime rate,” as defined in the Loan Agreement, minus 3%.

As of October 31, 2018, the Company had not drawn down from the facility and the Loan Agreement expired on October 31, 2018.

In connection with the Loan Agreement, the Company agreed to issue a warrant to the lender for the purchase of up to 188,702 shares of the Company’s Series A Preferred Stock with an exercise price of $0.7949 per share. The warrant expires on June 22, 2027. The warrant was initially exercisable for the purchase of up to 28,305 shares of Series A Preferred Stock and could become exercisable for up to an additional 160,397 shares of Series A Preferred Stock based on the amounts drawn under the Loan Agreement. On the issuance date of the warrant, the Company recorded a deferred financing cost and a liability for the warrant to purchase preferred stock in the Company’s consolidated balance sheet equal to the issuance-date fair value of the warrant. Upon closing of the IPO, the carrying amount of the warrant to purchase preferred stock as of the date of IPO was transferred to the account of additional paid in capital (Note 3).

The Company recognized a loss of $162 in the consolidated statements of operations and comprehensive loss for the year ended December 31, 2018 related to the change in fair value of the warrant. On July 13, 2018, the lender of the Loan Agreement exercised its common stock warrants to purchase 6,850 shares of common stock on a net basis, resulting in the issuance of 6,091 shares of common stock.

8. Redeemable Convertible Preferred Stock

Prior to the IPO, the authorized capital stock of the Company included 63,491,857 shares of $0.0001 par value preferred stock, of which 3,333,333 shares have been designated as Series Seed Preferred Stock, 31,639,202 shares have been designated as Series A Preferred Stock and 28,519,322 shares have been designated as Series B Preferred Stock.

On January 19, 2018, the Company entered into a stock purchase agreement for the sale of 28,285,557 shares of Series B Preferred Stock for $2.1389 per share. The total gross proceeds received were $60,500 and issuance costs were $2,243. In addition, the Company issued 233,765 shares of Series B Preferred Stock to BioMarin as required by the Company’s license agreement with BioMarin (Note 11).

Upon closing of the IPO, all outstanding shares of Preferred Stock were converted into 15,320,213 shares of common stock. The holders of the Company’s Preferred Stock had certain voting, dividend, and redemption rights, as well as liquidation preferences and conversion privileges. All rights, preferences, and privileges associated with the preferred stock were terminated at the time of the Company’s IPO in conjunction with the conversion of all outstanding shares of Preferred Stock into shares of common stock.

9. Common Stock

As of December 31, 2019 and 2018, the authorized capital stock of the Company included 150,000,000 shares of common stock, $0.0001 par value, and 10,000 shares of undesignated preferred stock. As of December 31, 2019 and 2018, no undesignated shares of preferred stock were outstanding.

In accordance to the Fourth Amended and Restated Certificate of Incorporation, the holders of the common stock shall have the exclusive right to vote for the election of directors of the Company and on all other matters requiring stockholder action, each outstanding share entitling the holder thereof to one vote on each matter properly submitted to the stockholders of the Company for their vote; provided, however, that, except as otherwise required by law, holders of common stock, as such, shall not be entitled to vote on any amendment to any amendment to a certificate of designations of any series of undesignated preferred stock that alters or changes the powers, preferences, rights or other terms of one or more outstanding series of undesignated preferred stock if the holders of such affected series of undesignated preferred stock are entitled to vote, either separately or together with the holders of one or more other such series, on such amendment pursuant to a certificate of designations of any series of undesignated preferred stock.

Through December 31, 2019, no cash dividends have been declared or paid.

(amounts in thousands, except share and per share data)

Initial Public Offering

On June 20, 2018, the Company's registration statement on Form S-1 relating to its IPO was declared effective by the SEC. The IPO closed on June 25, 2018 and the Company issued and sold 5,247,958 common shares at a public offering price of $19.00 per share for net proceeds of $90,103 after deducting underwriting discounts and commissions of $6,980 and other offering expenses of approximately $2,628. Simultaneously, on June 25, 2018, the Company issued and sold 787,193 additional common shares, pursuant to the full exercise of the underwriters' option to purchase additional shares, for net proceeds of $13,910 after deducting underwriting discounts and commissions of $1,047. The aggregate net proceeds to the Company from the IPO, after deducting underwriting discounts and commissions and other offering costs, were $104,013.

Follow-On Public Offering

In July 2019, the Company closed an underwritten public offering of 7,475,000 shares of its common stock at a public offering price of $18.50 per share, which included 975,000 shares of the Company's common stock resulting from the full exercise of the underwriters' option to purchase additional shares at the public offering price, less underwriting discounts and commissions (the "July 2019 Follow-on Offering"). The net proceeds to the Company from the July 2019 Follow-on Offering, after deducting underwriting discounts and commissions and other offering expenses payable by the Company, were approximately $129,500.

Common Stock Reserved for Future Issuance

At December 31, 2019 and 2018, the Company has reserved the following shares of common stock for future issuance:

	December 31,	
	2019	2018
Shares reserved for vesting of restricted stock awards	30,252	153,276
Shares reserved for exercise of outstanding stock options	3,414,445	2,164,101
Shares reserved for vesting of restricted stock units	2,300	
Shares reserved for issuance under the 2018 Stock Option and Incentive Plan	332,513	385,561
Shares reserved for issuance under the 2018 Employee Stock Purchase Plan	459,595	223,200
Shares reserved for issuance under the 2019 Inducement Plan	1,800,000	—
Total shares of authorized common stock reserved for future issuance	6,039,105	2,926,138

10. Stock-Based Compensation

Amended and Restated 2015 Stock Option and Grant Plan

The Company's Amended and Restated 2015 Stock Option and Grant Plan, (the "2015 Plan") provides for the Company to issue restricted stock awards and restricted stock units, or to grant incentive stock options or non-statutory stock options. Incentive stock options may be granted only to the Company's employees including officers and members of the Board who are also employees. Restricted stock awards and restricted stock units and non-statutory stock options may be granted to employees, members of the Board, outside advisors, and consultants of the Company.

The total number of common shares that may be issued under the 2015 Plan was 2,008,564 shares. Following the IPO, no further grants will be made under 2015 plan.

Shares that expire, are terminated, surrendered or canceled under the 2015 Plan without having been fully exercised will be available for future awards under the 2018 Plan (as defined below). In addition, shares of common stock that are tendered to the Company by a participant to exercise an award are added to the number of shares of common stock available for future awards.

The 2015 Plan is administered by the Board. Equity awards granted to employees and members of the Board typically vest over four years.

2018 Stock Option and Incentive Plan

The Company's 2018 Stock Option and Incentive Plan (the "2018 Plan") was adopted by the Board on June 1, 2018 and approved by stockholders on June 7, 2018 and became effective upon the effectiveness of the Company's Registration Statement on Form S-1. The 2018 Plan replaced the 2015 Plan as the Board determined not to make additional awards under the 2015 Plan following the pricing of the Company's IPO. The 2018 Plan allows the Board, compensation committee or other designated committee to make equity-based and cash-based incentive awards to its officers, employees, directors and other key persons (including consultants).

The Company initially reserved 616,300 shares of its common stock for the issuance of awards under the 2018 Plan. The 2018 Plan provides that the number of shares reserved and available for issuance under the plan will automatically increase each January 1, beginning on January 1, 2019, by 4% of the outstanding number of shares of our common stock on the immediately preceding December 31, or such lesser number of shares as determined by its Board or compensation committee (the "Plan Evergreen"). This number is subject to adjustment in the event of a stock split, stock dividend or other change in its capitalization.

The number of options available for future grant under the 2018 Plan was 332,513 as of December 31, 2019, which does not include the shares added to the 2018 Plan reserve on January 1, 2020 as a result of the Plan Evergreen for the year ended December 31, 2019.

During the years ended December 31, 2019 and 2018, the Company granted options to purchase 1,677,967 and, 1,277,528 shares, respectively, of common stock to employees, nonemployees and members of the Board.

2018 Employee Stock Purchase Plan

The Company's 2018 Employee Stock Purchase Plan (the "ESPP") was adopted by the Board on June 1, 2018 and approved by stockholders on June 7, 2018 and became effective upon the effectiveness of the Company's Registration Statement on Form S-1. The ESPP is intended to qualify as an "employee stock purchase plan" within the meaning of Section 423(b) of the Code. The ESPP initially reserves and authorizes the issuance of up to a total of 223,200 shares of common stock to participating employees. The ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2019 and each January 1 thereafter through January 1, 2028, by the least of (i) 1% of the outstanding number of shares of our common stock on the immediately preceding December 31; (ii) 1,115,700 shares or (iii) such number of shares as determined by the ESPP administrator (the "ESPP Evergreen"). The number of shares reserved under the ESPP is subject to adjustment in the event of a stock split, stock dividend or other change in our capitalization.

During the years ended December 31, 2019 and 2018, the Company issued 1,671 and 0 shares, respectively of common stock. The total number of common shares that may be issued under the ESPP was 461,266 shares as of December 31, 2019, of which 459,595 shares remained available for future grant, and which does not include the shares added to the ESPP reserve on January 1, 2020 as a result of the ESPP Evergreen for the year ended December 31, 2019.

2019 Inducement Plan

The Company's 2019 Inducement Plan (the "2019 Plan") was adopted by the Board on December 11, 2019. The purpose of the 2019 Plan is to allow the Company to grant equity awards to new employees as inducements material to such new employee's acceptance of employment with the Company. The Company intends that the shares underlying the 2019 Plan be reserved for persons to whom the Company may issue securities without stockholder approval as an inducement pursuant to Rule 5635(c)(4) of the Nasdaq marketplace rules.

The Company initially reserved 1,800,000 shares of its common stock for the issuance of awards under the 2019 Plan.

The number of options available for future grant under the 2019 Plan was 1,800,000 as of December 31, 2019.

(amounts in thousands, except share and per share data)

Stock Option Valuation

The assumptions that the Company used to determine the grant-date fair value of stock options granted to employees and members of the Board were as follows, presented on a weighted-average basis:

	Year Ended December 31,	
	2019	2018
Expected option life (years)	5.62	6.06
Risk-free interest rate	2.09%	2.74%
Expected volatility	76.83%	81.60%
Expected dividend yield	—%	—%

The following table summarizes the Company's stock option activity for the year ended December 31, 2019:

	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding as of December 31, 2018	2,164,101	$ 7.75	8.77	$ 23,083
Granted	1,667,967	$ 16.50		
Exercised	(236,483)	$ 2.12		
Cancelled or forfeited	(181,140)	$ 14.13		
Outstanding as of December 31, 2019	3,414,445	$ 12.08	8.43	$ 29,353
Exercisable as of December 31, 2019	977,229	$ 5.69	7.26	$ 14,702

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the underlying stock options and the estimated fair value of the Company's common stock for those stock options that had exercise prices lower than the estimated fair value of the Company's common stock.

The aggregate intrinsic value of options exercised during the years ended December 31, 2019 and 2018 was $3,514 and $410, respectively.

The weighted-average grant-date fair value of the Company's stock options granted during the years ended December 31, 2019 and 2018 was $11.61 and $10.91, respectively.

Restricted Common Stock

The Company has granted restricted common stock with time-based vesting conditions to certain employees of the Company. The purchase price of the restricted stock awards are determined by the Board. Unvested shares of restricted common stock may not be sold or transferred by the holder. These restrictions lapse according to the time-based vesting conditions of each award. The Company has the option to repurchase the restricted stock awards at the original purchase price if the grantee terminates its working relationship with the Company prior to the vesting date.

(amounts in thousands, except share and per share data)

The following table summarizes the Company's restricted common stock activity for the year ended December 31, 2019:

	Number of Shares	Weighted-Average Grant Date Fair Value
Issued and unvested as of December 31, 2018	153,275	$ 0.42
Granted	2,300	$ 15.65
Vested	(123,023)	$ 0.42
Forfeited, canceled or expired	—	$ —
Issued and unvested as of December 31, 2019	32,552	$ 1.50

The total fair value of restricted common stock vested during the years ended December 31, 2019 and 2018 was $50 and $52, respectively.

Stock-Based Compensation

Stock-based compensation expense was allocated as follows:

	Year Ended December 31,	
	2019	2018
Research and development	$ 3,646	$ 920
General and administrative	3,154	1,276
Total stock-based compensation expense	$ 6,800	$ 2,196

As of December 31, 2019, total unrecognized compensation cost related to unvested stock-based awards was $22,878, which is expected to be recognized over a weighted-average period of 3.14 years.

11. License Agreements

Agreements with UHN

Fabry License Agreement—

On January 27, 2016, the Company entered into an agreement with UHN, pursuant to which UHN granted the Company an option to enter into an exclusive license under the UHN intellectual property related to Fabry disease in accordance with the pre-negotiated licensing terms. On November 4, 2016, the Company exercised its option and entered into a license agreement with UHN, pursuant to which UHN granted the Company an exclusive worldwide license under certain intellectual property rights and a non-exclusive worldwide license under certain know-how, in each case subject to certain retained rights, to develop, commercialize and sell products for use in the treatment of Fabry disease. In addition, for three years following the execution of the agreement, UHN granted the Company an exclusive option to obtain a license under certain improvements to the licensed intellectual property rights as well as an option to negotiate a license under certain other improvements.

Under this agreement, the Company paid an option fee of CAD $20, an upfront license fee of CAD $75, plus the annual license maintenance fee for the first year. Thereafter, the Company is also required to pay UHN future annual license maintenance fees until the first sale of a licensed product in certain markets. The Company is also obligated to make future milestone payments in an aggregate amount of up to CAD $2,450 upon the achievement of specified milestones as well as royalties on a country-by-country basis of a low to mid-single-digit percentage of annual net sales of licensed products and a lower single-digit royalty percentage in certain circumstances. Additionally, the Company has agreed to pay a low double-digit royalty percentage of all sublicensing revenue.

The agreement requires the Company to meet certain performance milestones within specified timeframes. UHN may terminate the agreement if the Company fails to meet these performance milestones despite using commercially reasonable efforts and the Company is unable to reach agreement with UHN on revised timeframes. The Company's royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration or termination of the last valid claim under the licensed intellectual property rights in such country, the tenth anniversary of the first commercial sale of such licensed product in such country and the expiration of any applicable regulatory exclusivity in such country.

Unless terminated earlier, the agreement expires upon the expiration of the Company's royalty obligation for all licensed products. UHN can terminate the agreement if the Company fails to make any payments within a specified period after receiving written notice of such failure, or in the event that the Company fails to obtain or maintain insurance. Either the Company or UHN may terminate the license agreement in the event of a material breach by the other party and failure to cure such breach within a certain period of time. The Company can voluntarily terminate the agreement with prior notice to UHN.

For the years ended December 31, 2019 and 2018, the Company recorded research and development expense related to this agreement with UHN of $783 and $15, respectively, which consists of reimbursable funded study trial costs and license maintenance fees. No milestone fees were incurred related to the Fabry license agreement in the years ended December 31, 2019 and 2018.

Interleukin 12 License Agreement—

On January 27, 2016, the Company entered into an exclusive license agreement with UHN, pursuant to which UHN granted the Company a license to certain patent rights for the commercial development, manufacture, distribution and use of any products or processes resulting from development of those patent rights related to Interleukin 12. Upon execution of this agreement, the Company paid an upfront license fee of CAD $264. In addition, as part of the initial consideration for the license, the Company issued to UHN 1,161,665 shares of the Company's common stock. The fair value of the shares issued to UHN of $480 and the upfront fee was expensed upon the execution of the agreement. In addition, the Company agreed to pay UHN up to $2,000 upon the closing of an IPO if certain criteria are met. This obligation was considered a derivative instrument and was initially recorded at fair value of $49 (Note 3). The Company is also required to pay UHN future annual license maintenance fees of CAD $50 on each anniversary of the effective date of the license agreement prior to expiration or termination and potential future milestone payments of up to CAD $19,275 upon the achievement of specified clinical and regulatory milestones. The Company also agreed to pay UHN royalties of a low single-digit percentage of net sales of licensed products sold by the Company. If the Company grants any sublicense rights under the license agreement, the Company has agreed to pay UHN a low double-digit royalty percentage of any sublicense income received by the Company.

The agreement requires the Company to meet certain diligence requirements based upon specified milestones. The agreement expires on the later of the date the last patent rights expire in the last country or ten years from the date of first sale. UHN can terminate the agreement if the Company fails to make any payments within a specified period after receiving written notice of such failure, or in the event that the Company fails to obtain or maintain insurance. The Company can voluntarily terminate the agreement with prior notice to UHN. Either the Company or UHN may terminate the license agreement in the event of a material breach by the other party and failure to cure such breach within a certain period of time.

For the years ended December 31, 2019 and 2018, the Company recorded research and development expense related to this agreement with UHN of $38 and $41, respectively, which consists of license maintenance fees. No milestone fees were incurred related to the Interleukin 12 license agreement in the years ended December 31, 2019 and 2018.

Agreement with BioMarin Pharmaceutical Inc. ("BioMarin")

On August 31, 2017, the Company entered into a license agreement with BioMarin, pursuant to which BioMarin granted the Company an exclusive worldwide license under certain intellectual property rights owned or controlled by BioMarin to develop, commercialize and sell products for use in the treatment of Pompe disease. The license agreement was amended in February 2018 and again in January 2020 to, among things, provide that BioMarin would supply the Company with certain technology materials. As consideration for this agreement, the Company paid an upfront license fee of $500 in cash and issued 233,765 shares of Series B Preferred Stock to BioMarin at the time of the Company's Series B Preferred Stock financing in January 2018. Both the upfront cash payment of $500 and the value of the shares Series B Preferred Stock issued of $500 were recorded as research and development expense during the year ended December 31, 2017. The Company is also obligated to make future milestone payments of up to $13,000 upon the achievement of certain specified milestones and agreed to pay BioMarin royalties of a low single-digit percentage of net sales of licensed products sold by the Company or its affiliates covered by patent rights in a relevant country. The Company recorded research and development expense related to this agreement with BioMarin of $1,000 related to the license for the year ended December 31, 2017. No expenses related to the license were recorded for the years ended December 31, 2019 and 2018.

Unless terminated earlier, the agreement expires upon the expiration of the Company's royalty obligation for all licensed products throughout the world. BioMarin and the Company can terminate the agreement in the event of a material breach by the other party and failure to cure such breach within a certain period of time. The Company may terminate the agreement at will upon written notice to BioMarin. BioMarin has the right to terminate the agreement upon the Company's bankruptcy or insolvency, or in the event of any challenge or opposition to the licensed patent rights or related actions brought by the Company or its affiliates or sublicensees, or if the Company, its affiliates or sublicensees knowingly assist a third-party in challenging or otherwise opposing the licensed patent rights, except as required under a court order or subpoena.

Agreement with GenStem Therapeutics, Inc. ("GenStem")

On October 2, 2017, the Company entered into a license agreement with GenStem, pursuant to which GenStem granted the Company an exclusive worldwide license, subject to certain retained rights, under certain intellectual property rights owned or controlled by GenStem to develop, commercialize and sell products for use in the treatment of cystinosis. Under this agreement, the Company paid an upfront license fee of $1,000 and is required to make payments upon completion of certain milestones up to an aggregate of $16,000. The Company also agreed to pay GenStem a tiered mid to high single-digit royalty percentage on annual net sales of licensed products as well as a low double-digit percentage of sublicense income received from certain third-party licensees. The Company's royalty obligation expires on a licensed product-by-licensed product and country-by-country basis on the eleventh anniversary of the first commercial sale of such licensed product in such country or the expiration of the last valid claim under the licensed patent rights covering such licensed product in such country, whichever is later. Unless terminated earlier, the agreement expires upon the expiration of the Company's royalty obligation for all licensed products throughout the world. GenStem and the Company can terminate the agreement in the event of a material breach by the other party and failure to cure such breach within a certain period of time. The Company may terminate the agreement at will upon the specified prior written notice to GenStem. The Company recorded research and development expense of $1,000 for the year ended December 31, 2017, which consisted of upfront fees related to the license.

For the year ended December 31, 2019, the Company recorded research and development expense of $2,000 , which related to milestone payments. No expense related to the license was recorded for the year ended December 31, 2018.

Agreement with Lund University Rights Holders

On November 17, 2016, the Company entered into a license agreement with affiliates of Lund University, along with certain other relevant rights holders that may be added from time to time, pursuant to which such rights holders granted to the Company an exclusive worldwide license, subject to certain retained rights, under certain intellectual property rights to develop, commercialize and sell products in any and all uses relevant to Gaucher disease. As consideration for the license, the Company is required to make payments in connection with the achievement of certain milestones up to an aggregate of $550. The agreement expires on the latest of (i) the twentieth anniversary of the end of a certain research project the Company is funding pursuant to an agreement with Lund University, (ii) the expiration of the term of any patent filed on the licensed rights that covers a licensed product, (iii) the expiration of any applicable marketing exclusivity right and (iv) such time that neither the Company nor any sublicensees, partners or contractors are commercializing a licensed product. Either the Company or the rights holders acting together may terminate the license agreement if the other such party commits a material breach and fails to cure such breach within a certain period of time, or if the other party enters into liquidation, becomes insolvent, or enters into composition or statutory reorganization proceedings. No expenses related to the license were recorded for the years ended December 31, 2019 and 2018.

(amounts in thousands, except share and per share data)

12. Income Taxes

For the years ended December 31, 2019 and 2018, the Company did not record a current or deferred income tax expense or (benefit) due to current and historical losses incurred by the Company. The Company's operations are predominantly based in the United States and the Company's foreign subsidiaries generated *de minimis* losses for the years ended December 31, 2019 and 2018.

A reconciliation of income tax expense (benefit) computed at the statutory federal income tax rate to the Company's effective tax rate as reflected in the consolidated financial statements is as follows:

	Year Ended December 31,	
	2019	2018
Federal income tax expense at statutory rate	21.0%	21.0%
State income taxes, net of federal benefit	5.2%	5.2%
Permanent differences	-0.9%	-0.8%
U.S.—TCJA	0.0%	0.0%
Foreign rate differential	0.2%	0.2%
Research and development tax credits	2.1%	1.1%
Change in valuation allowance	-27.6%	-26.5%
Provision to Return	0.0%	-0.2%
Effective income tax rate	0.0%	0.0%

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets and liabilities are comprised of the following:

	December 31,	
	2019	2018
Deferred tax assets:		
U.S., foreign and state net operating loss carryforwards	$ 33,594	$ 15,815
Research and development credits	1,716	454
Capitalized start up and organizational costs	32	35
Equity based compensation	543	185
Derivative liability	—	—
Licensing agreements	1,756	1,258
Accruals and other	993	948
Total deferred tax assets	38,634	18,695
Valuation allowance	(38,425)	(18,457)
Net deferred tax assets	$ 209	$ 238
Deferred tax liabilities:		
Property and equipment	$ (209)	$ (238)
Total deferred tax liabilities	$ —	$ —

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. As of December 31, 2019 and 2018, based on the Company's history of operating losses, the Company has concluded that it is not more likely than not that the benefit of its deferred tax assets will be realized. Accordingly, the Company has provided a full valuation allowance for deferred tax assets as of December 31, 2019 and 2018. The valuation allowance increased $19,968 and $11,991 during the years ended December 31, 2019 and 2018, respectively, due primarily to net operating losses generated.

As of December 31, 2019 and 2018, the Company had U.S. federal net operating loss carryforwards of $121,836 and $57,279, respectively, that may be available to offset future income tax liabilities. The U.S. federal tax operating loss carryforwards of approximately $17,743 will expire at various dates through 2037. Approximately $104,093 of the U.S. federal tax operating losses can be carried forward indefinitely. As of December 31, 2019 and 2018, the Company also had U.S. state net operating loss carryforwards of $115,129 and $54,212, respectively, which may be available to offset future taxable income. These losses expire at various dates through 2039. As of December 31, 2019 and 2018, the Company had foreign net operating loss carryforwards of $2,440 and $1,201, respectively. The foreign net operating losses can be carried forward indefinitely.

As of December 31, 2019 and 2018, the Company has federal research and development tax credit carryforwards of $1,547 and $339, respectively. Included in the $1,547 of federal tax credit carryforwards are $530 of orphan drug credits. The Company qualifies for, and has elected to, apply part of its federal research credits against its payroll tax liability in accordance with certain provisions of the Internal Revenue Code. The amount applied towards the Company's payroll tax liability is capped at $250 per year. The federal research credits generated in excess of the $250 cap are able to be carried forward for 20 years. As of December 31, 2019 and 2018, the Company had state research and development tax credit carryforwards of approximately $214 and $146, respectively, available to reduce future tax liabilities which expire at various dates through 2033. For all years through December 31, 2019, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards.

As the Company carries out extensive research and development activities, it seeks to benefit from the Australian research and development tax credit cash rebate regime. Under this regime, the Company's Australian subsidiary, AVROBIO Australia, may be eligible to surrender the trading losses that arise from its research and development activities for a payable tax credit of up to approximately 43.5% of eligible research and development expenditures. Qualifying expenditures largely comprise employment costs for research staff, consumables, certain internal overhead costs and subcontracted expenditures as part of research projects for which the Company does not receive income. For the year ended December 31, 2019, the Company recorded $0.9 million in research and development tax credits as an offset to research and development expenses.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed numerous financings since its inception, which may have resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code, or could result in a change in control in the future.

The Company files income tax returns in the United States, Australia and Canada, and in several states. The foreign, federal and state income tax returns are generally subject to tax examinations for the tax years ended December 31, 2016 through December 31, 2018. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by foreign tax authorities, the Internal Revenue Service, or state tax authorities to the extent utilized in a future period.

(amounts in thousands, except share and per share data)

13. Net Loss per Share Attributable to Common Stockholders

For purposes of the diluted net loss per share calculation, stock options and unvested restricted stock are considered to be common stock equivalents but have been excluded from the calculation of diluted net loss per share, as their effect would be anti-dilutive for all periods presented. Therefore, the weighted-average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same.

The following potentially dilutive common stock equivalents, presented based on amounts outstanding at each period end, were excluded from the computation of diluted net loss per share attributable to common stockholders for the periods indicated:

	Year Ended December 31,	
	2019	2018
Options to purchase common stock	3,414,445	2,164,101
Restricted common stock	32,552	153,276

14. Commitments and Contingencies

Lease Agreements

In August 2017, the Company entered into a sub-lease agreement for laboratory space located in Cambridge Massachusetts, United States, which expires in August 2020. The annual lease payments are subject to a 3% increase each year. The Company recognizes rent expense on a straight-line basis over the lease period and has recorded deferred rent for rent expense incurred but not yet paid. On December 4, 2018, the Company terminated the sub-lease without any penalty. The leasehold improvement cost was written off to rental expenses during the year ended December 31, 2018.

On January 12, 2018, the Company entered into a lease agreement for office space located in Cambridge, Massachusetts. The lease agreement expires in January 2023, with a landlord who is an affiliate of the landlord of the Company’s prior lease facility. The annual lease payments are subject to a 3% increase each year. The Company recognizes rent expense on a straight-line basis over the lease period and has recorded deferred rent for rent expense incurred but not yet paid. The Company received a tenant incentive allowance of $842 in 2018. Such incentive allowance is being amortized as a reduction of rent expense on a straight-line basis over the lease period. In accordance with the lease agreement, the Company is required to maintain a security deposit of $209, which was recorded in other assets as of December 31, 2019 and 2018. In contemplation of this agreement, the Company terminated its prior lease agreement.

On August 31, 2018, the Company entered into a sub-lease agreement for lab space located in Cambridge Massachusetts, United States, which expires in October 2020. The annual lease payments are subject to a 3% increase each year. In accordance with the lease agreement, the Company is required to maintain a security deposit of $283, which was recorded in other assets as of December 31, 2019 and 2018.

The Company recorded rent expense of $2,257 and $1,295 during the years ended December 31, 2019 and 2018, respectively.

The following table summarizes the future minimum lease payments due under operating leases as of December 31, 2019:

Year Ending December 31,	
2020	$ 1,563
2021	705
2022	726
2023	61
	$ 3,055

Legal Proceedings

The Company, from time to time, may be party to litigation arising in the ordinary course of business. The Company was not subject to any material legal proceedings during the years ended December 31, 2019 and 2018, and to the best of its knowledge, no material legal proceedings are currently pending or threatened.

Other

The Company is also party to various agreements, principally relating to licensed technology, that require future payments relating to milestones not met at December 31, 2019 and 2018, or royalties on future sales of specified products. No milestone or royalty payments under these agreements are expected to be payable in the immediate future. See Note 11 for discussion of these arrangements.

The Company enters into standard indemnification agreements in the ordinary course of business. Pursuant to the agreements, the Company agrees to indemnify, hold harmless, and to reimburse the indemnified party for losses suffered or incurred by the indemnified party, generally the Company's business partners, in connection with any U.S. patent or any copyright or other intellectual property infringement claim by any third-party with respect to the Company's products. The term of these indemnification agreements is generally perpetual any time after execution of the agreement. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is unlimited. The Company has never incurred costs to defend lawsuits or settle claims related to these indemnification agreements.

15. Related Party Transactions

UHN

In connection with the Company's entry into a license agreement with UHN on January 27, 2016, the Company issued UHN 1,161,665 shares of its common stock. Upon the closing of the IPO, as UHN's fully-diluted percentage ownership of the Company was reduced within a range of specified percentages, the Company was obligated to pay UHN an amount of $2,000, which was paid in July 2018. See Note 3 for further discussion on the accounting treatment for this provision.

For the years ended December 31, 2019 and 2018, the Company recognized $821 and $56, respectively, of research and development expense related to the license agreements with UHN. Refer to Note 11 for additional information regarding the UHN license agreements.

Others

For the years ended December 31, 2019 and 2018, the Company recorded expenses of $1,451 and $348, respectively, related to a sublease to rent lab space, provided by an entity affiliated with a member of the board.

For the years ended December 31, 2019 and 2018, the Company recorded expenses of $0 and $40, respectively, related to consulting services provided by an entity affiliated with an officer of the Company and a member of the Board.

16. Benefit Plans

The Company established a defined contribution savings plan under Section 401(k) of the Internal Revenue Code. This plan covers substantially all employees who meet minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pre-tax basis. In August 2018, the Company's Board approved a company matching contribution of up to 3%, effective October 1, 2018. The Company made matching contributions of $224 and $35 to the plan during the years ended December 31, 2019 and 2018, respectively.

17. Subsequent Events

On December 20, 2019, the Company filed a shelf registration statement on Form S-3 with the SEC (the "December 2019 Shelf," which covers the offering, issuance and sale by the Company of up to an aggregate of $250.0 million of the Company's common stock, preferred stock, debt securities, warrants and/or units. The December 2019 Shelf was declared effective by the SEC on January 14, 2020.

In February 2020, the Company closed an underwritten public offering of 4,350,000 shares of its common stock at a public offering price of $23.00 per share, less underwriting discounts and commissions. The net proceeds to the Company from this offering, after deducting underwriting discounts and commissions and other estimated offering expenses payable by the Company, were approximately $93,547.

EXHIBIT NO.	EXHIBIT INDEX
3.1	Fourth Amended and Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1 to the Registrant's Current Report on Form 8-K filed on June 25, 2018 (File No. 001-38537) and incorporated herein by reference)
3.2	Amended and Restated By-laws (filed as Exhibit 3.2 to the Registrant's Current Report on Form 8-K filed on June 25, 2018 (File No. 001-38537) and incorporated herein by reference)
4.1	Form of Specimen Common Stock Certificate (filed as Exhibit 4.1 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
4.2	Second Amended and Restated Investors' Rights Agreement among the Registrant and certain of its stockholders, dated January 9, 2018 (filed as Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)
4.3	Description of Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934, as amended
10.1#	2015 Amended and Restated Stock Option and Grant Plan, as amended, and forms of award agreements thereunder (filed as Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)
10.2#	2018 Stock Option and Incentive Plan and forms of award agreements thereunder (filed as Exhibit 10.2 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.3#	Senior Executive Cash Incentive Bonus Plan (filed as Exhibit 10.3 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.4#	Form of Indemnification Agreement (filed as Exhibit 10.4 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.5†	Exclusive License Agreement, by and between the Registrant and University Health Network, dated November 4, 2016, as amended (filed as Exhibit 10.5 to the Registrant's First Amendment to the Registration Statement on Form S-1 filed on June 1, 2018 (File No. 333-225213) and incorporated herein by reference)
10.6†	License Agreement, by and between the Registrant and BioMarin Pharmaceutical Inc., dated August 31, 2017 (filed as Exhibit 10.6 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.7††	Amendment No. 1 to License Agreement, by and between the Registrant and BioMarin Pharmaceutical Inc., dated February 21, 2018
10.8††	Amendment No. 2 to License Agreement, by and between the Registrant and BioMarin Pharmaceutical Inc., dated January 7, 2020
10.9†	Exclusive License Agreement, by and among the Registrant, Stefan Karlsson and Maria Dahl, dated January 30, 2017 (filed as Exhibit 10.7 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)
10.10†	License Agreement, by and between the Registrant and GenStem Therapeutics, Inc., dated October 2, 2017 (filed as Exhibit 10.8 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)
10.11#	Amended and Restated Employment Agreement, by and between the Registrant and Geoff MacKay, effective as of June 25, 2018 (filed as Exhibit 10.9 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.12#	Employment Agreement, by and between the Registrant and Erik Ostrowski, dated December 17, 2018 (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on December 21, 2018 (File No. 001-38537) and incorporated herein by reference)

EXHIBIT NO.	EXHIBIT INDEX
10.13#	Employment Agreement, by and between the Registrant and Steven Avruch, dated December 17, 2018 (filed as Exhibit 10.13 to the Registrant's Annual Report on Form 10-K filed on March 25, 2019 (File No. 001-38537) and incorporated herein by reference)
10.14#	Consulting Agreement, by and between the Registrant and Birgitte Volck, M.D., Ph.D., dated December 17, 2018 (filed as Exhibit 10.14 to the Registrant's Annual Report on Form 10-K filed on March 25, 2019 (File No. 001-38537) and incorporated herein by reference)
10.15#	Employment Agreement, by and between the Registrant and Birgitte Volck, M.D., Ph.D., dated December 17, 2018 (filed as Exhibit 10.15 to the Registrant's Annual Report on Form 10-K filed on March 25, 2019 (File No. 001-38537) and incorporated herein by reference)
10.16#	Employment Agreement, by and between the Registrant and Deanna Petersen, dated September 1, 2018
10.17#	2018 Employee Stock Purchase Plan (filed as Exhibit 10.14 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.18	Lease Agreement, dated as of January 12, 2018, by and between the Registrant and ARE-MA Region No. 59, LLC (filed as Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)
10.19#	2019 Inducement Plan and form of award agreement thereunder (filed as Exhibit 99.1 to the Registrant's Registration Statement on Form S-8 filed on December 20, 2019 (File No. 333-235643) and incorporated herein by reference)
10.20#	Form of Inducement Stock Option Award (filed as Exhibit 99.1 to the Registrant's Registration Statement on Form S-8 filed on March 25, 2019 (File No. 333-230493)) and incorporated herein by reference)
21.1	Subsidiaries of the Registrant
23.1	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1*	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

† Confidential treatment has been granted for portions of this Exhibit pursuant to Rule 406 promulgated under the Securities Act of 1933, as amended.
†† Portions of this exhibit have been omitted because they are both (i) not material and (ii) would likely cause competitive harm to the registrant if publicly disclosed.
# Indicates a management contract or any compensatory plan, contract or arrangement.
* Indicates the exhibit is being furnished, not filed, with this report.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized on the 16th day of March, 2020.

AVROBIO, INC.

By: /s/ Geoff Mackay
Geoff MacKay
President and Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Geoff MacKay and Erik Ostrowski, and each of them, his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this report, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or either of them, or their or his substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed by the following persons on behalf of the registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Geoff MacKay Geoff MacKay	President, Chief Executive Officer and Director *(Principal Executive Officer)*	March 16, 2020
/s/ Erik Ostrowski Erik Ostrowski	Chief Financial Officer *(Principal Financial Officer and Principal Accounting Officer)*	March 16, 2020
/s/ Bruce Booth Bruce Booth, D.Phil.	Chairman of the Board of Directors	March 16, 2020
/s/ Ian T. Clark Ian T. Clark	Director	March 16, 2020
/s/ Phillip B. Donenberg Phillip B. Donenberg	Director	March 16, 2020
/s/ Annalisa Jenkins Annalisa Jenkins, M.B.B.S., F.R.C.P	Director	March 16, 2020
/s/ Christopher Paige Christopher Paige, Ph.D.	Director	March 16, 2020
/s/ Philip J. Vickers Philip J. Vickers, Ph.D.	Director	March 16, 2020

Exhibit 4.3

Description of the Registrant's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934, as amended

The common stock, par value $0.0001 per share ("Common Stock"), of AVROBIO, Inc., a Delaware corporation (the "Company," "us," "we," or "our"), is registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). The following description of the Common Stock sets forth certain general terms and provisions of the Common Stock. These descriptions are in all respects subject to and qualified in their entirety by, and should be read in conjunction with, the applicable provisions of the Fourth Amended and Restated Certificate of Incorporation of the Company (the "Charter") and the Amended and Restated By-laws of the Company (the "Bylaws") (each of which is incorporated herein by reference and copies of which are incorporated by reference as exhibits to our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission) and the applicable provisions of the Delaware General Corporation Law ("DGCL").

Authorized Capital Stock

Our authorized capital stock consists of 150,000,000 shares of Common Stock and 10,000,000 shares of preferred stock, par value $0.0001 per share ("Preferred Stock"), all of which shares of Preferred Stock are undesignated.

Common Stock

Dividends

Holders of our Common Stock are entitled to receive ratably any dividends declared by our board of directors (the "Board") out of funds legally available for that purpose, subject to any preferential dividend rights of any outstanding Preferred Stock.

Voting

Holders of our Common Stock are entitled to one vote for each share held on all matters submitted to a vote of the stockholders. The holders of our Common Stock do not have any cumulative voting rights.

Distributions on Liquidation

In the event of our liquidation, dissolution or winding up, holders of our Common Stock will be entitled to share ratably in all assets remaining after payment of all debts and other liabilities and any liquidation preference of any outstanding Preferred Stock. All outstanding shares are fully paid and non-assessable.

Other Rights

Our Common Stock has no preemptive rights, conversion rights or other subscription rights or redemption or sinking fund provisions.

Registration Rights

Certain holders of our Common Stock are entitled to rights with respect to the registration of these securities under the Securities Act of 1933, as amended (the "Securities Act"). These rights are provided under the terms of an investors' rights agreement (the "Investors' Rights Agreement") between us and holders of our Preferred Stock, which was subsequently converted into Common Stock in connection with our initial public offering in June 2018 (the "IPO"). The Investors' Rights Agreement includes demand registration rights, short-form registration rights and piggyback registration rights. All fees, costs and expenses of underwritten registrations under this agreement will be borne by us and all selling expenses, including underwriting discounts and selling commissions, will be borne by the holders of the shares being registered.

Demand Registration Rights

The holders of 5,567,289 shares of our Common Stock are entitled to demand registration rights. Under the terms of the Investors' Rights Agreement, we will be required, upon the written request of holders of at least 50% of these securities that would result in an aggregate offering price of at least $10.0 million, to file a registration statement and use commercially reasonable efforts to effect the registration of all or a portion of these shares for public resale. We are required to effect only two registrations pursuant to this provision of the Investors' Rights Agreement.

Short-Form Registration Rights

Pursuant to the Investors' Rights Agreement, if we are eligible to file a registration statement on Form S-3, upon the written request of holders of at least 25% of these securities at an aggregate offer price of at least $3.0 million, we will be required to use commercially reasonable efforts to effect a registration of such shares. We are required to effect only two registrations in any twelve month period pursuant to this provision of the Investors' Rights Agreement. The right to have such shares registered on Form S-3 is further subject to other specified conditions and limitations.

Piggyback Registration Rights

Pursuant to the Investors' Rights Agreement, if we register any of our securities either for our own account or for the account of other security holders, the holders of these shares are entitled to include their shares in the registration. Subject to certain exceptions contained in the Investors' Rights Agreement, we and the underwriters may limit the number of shares included in the underwritten offering to the number of shares which we and the underwriters determine in our sole discretion will not jeopardize the success of the offering.

Indemnification

Our Investors' Rights Agreement contains customary cross-indemnification provisions, under which we are obligated to indemnify holders of registrable securities in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions attributable to them.

Expiration of Registration Rights

The demand registration rights and short form registration rights granted under the Investors' Rights Agreement will terminate on the earliest of (i) a deemed liquidation event, as defined in the Investors' Rights Agreement, (ii) the fifth anniversary of the completion of our IPO and (iii) when the holders' shares may be sold without restriction pursuant to Rule 144 of the Securities Act within a three month period.

Anti-Takeover Effects of our Charter and Bylaws and Delaware Law

Our Charter and Bylaws include a number of provisions that may have the effect of delaying, deferring or preventing another party from acquiring control of us and encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our Board rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

Board Composition and Filling Vacancies

Our Charter provides for the division of our Board into three classes serving staggered three-year terms, with one class being elected each year. Our Charter also provides that directors may be removed only for cause and then only by the affirmative vote of the holders of two-thirds or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our Board, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office even if less than a quorum. The classification of directors, together with the limitations on removal of directors and treatment of vacancies, has the effect of making it more difficult for stockholders to change the composition of our Board.

No Written Consent of Stockholders

Our Charter provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting. This limit may lengthen the amount of time required to take stockholder actions and would prevent the amendment of our Bylaws or removal of directors by our stockholders without holding a meeting of stockholders.

Meetings of Stockholders

Our Charter and Bylaws provide that only a majority of the members of our Board then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our Bylaws limits the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

Advance Notice Requirements

Our Bylaws establishes advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days nor more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. Our Bylaws specify the requirements as to form and content of all stockholders' notices. These requirements may preclude stockholders from bringing matters before the stockholders at an annual or special meeting.

Amendments to the Charter and Bylaws

Any amendment of our Charter must first be approved by a majority of our Board, and if required by law or our Charter, must thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, board composition, limitation of liability and the amendment of our Bylaws and Charter must be approved by not less than two-thirds of the outstanding shares entitled to vote on the amendment, and not less than two-thirds of the outstanding shares of each class entitled to vote thereon as a class. Our Bylaws may be amended by the affirmative vote of a majority of the directors then in office, subject to any limitations set forth in the Bylaws; and may also be amended by the affirmative vote of at least two-thirds of the outstanding shares entitled to vote on the amendment, or, if our Board recommends that the stockholders approve the amendment, by the affirmative vote of the majority of the outstanding shares entitled to vote on the amendment, in each case voting together as a single class.

Undesignated Preferred Stock

Our Charter provides for 10,000,000 authorized shares of Preferred Stock. The existence of authorized but unissued shares of Preferred Stock may enable our Board to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our Board were to determine that a takeover proposal is not in the best interests of our stockholders, our Board could cause shares of Preferred Stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our Charter grants our Board broad power to establish the rights and preferences of authorized and unissued shares of Preferred Stock. The issuance of shares of Preferred Stock could decrease the amount of earnings and assets available for distribution to holders of shares of Common Stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Choice of Forum

Our Bylaws provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any state law claim for: (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of or based on a fiduciary duty owed by any of our current or former directors, officers or other employees to us or our stockholders; (3) any action asserting a claim against us or any of our current or former directors, officers, employees or stockholders arising pursuant to any provision of the DGCL or our Charter or Bylaws; or (4) any action asserting a claim governed by the internal affairs doctrine (the "Delaware Forum Provision"). The Delaware Forum Provision will not apply to any causes of action arising under the Securities Act of 1933 or the Securities Exchange Act of 1934. Our Bylaws also provide that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock will be deemed to have notice of and to have consented to this choice of forum provision.

In addition, our Bylaws contains a provision by virtue of which unless we consent in writing to the selection of an alternative forum, the United States District Court for the District of Massachusetts will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (the "Federal Forum Provision"). If any action the subject matter of which is within the scope of the preceding sentence is filed in a court other than the United States District Court for the District of Massachusetts, the plaintiff or plaintiffs shall be deemed by this provision of our Bylaws (i) to have consented to removal of the action by us to the United States District Court for the District of Massachusetts, in the case of an action filed in a state court, and (ii) to have consented to transfer of the action to the United States District Court for the District of Massachusetts. We have chosen the United States Court for the District of Massachusetts as the exclusive forum for such causes of action because our principal executive offices are located in Cambridge, Massachusetts. Some companies that have adopted similar federal district court forum selection provisions are currently subject to a suit in the Court of Chancery of the State of Delaware by stockholders who assert that the federal district court forum selection provision is not enforceable. On December 19, 2018, the Court of Chancery of the State of Delaware issued a decision declaring that such federal forum selection provisions purporting to require claims under the Securities Act be brought in federal court are ineffective and invalid under Delaware law. In August 2019, the decision was appealed to the Delaware Supreme Court, and the appeal remains pending before the Delaware Supreme Court. Unless and until the Court of Chancery's decision is reversed by the Delaware Supreme Court or otherwise abrogated, we do not intend to enforce our federal forum selection provision designating the District of Massachusetts as the exclusive forum for Securities Act claims. In the event that the Delaware Supreme Court affirms the Court of Chancery's decision or otherwise determines that federal forum selection provisions are invalid, the Company's Board of Directors intends to amend promptly our Bylaws to remove our Federal Forum Provision. As a result of the Court of Chancery's decision or a decision by the Supreme Court of Delaware affirming the Court of Chancery's decision, we may incur additional costs associated with our Federal Forum Provision, which could have an adverse effect on our business, financial condition and results of operations.

We recognize that the Delaware Forum Provision and the Federal Forum Provision may impose additional litigation costs on stockholders in pursuing any such claims, particularly if the stockholders do not reside in or near the State of Delaware or the Commonwealth of Massachusetts. Additionally, the forum selection clauses in our Bylaws may limit our stockholders' ability to bring a claim in a judicial forum that they find favorable for disputes with us or our directors, officers or employees, which may discourage the filing of lawsuits against us and our directors, officers and employees even though an action, if successful, might benefit our stockholders. Alternatively, if the Federal Forum Provision is found inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could have an adverse effect on our business, financial condition or results of operations. The Court of Chancery of the State of Delaware or the United States District Court for the District of Massachusetts may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

Section 203 of the DGCL

We are subject to the provisions of Section 203 of the DGCL. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

- before the stockholder became interested, our Board approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and

  employee stock plans, in some instances, but not the outstanding voting stock owned by the interested stockholder; or

- at or after the time the stockholder became interested, the business combination was approved by our Board and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;

- any sale, transfer, lease, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;

- subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

- subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; and

- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

Nasdaq Global Select Market Listing

Our Common Stock is listed on The Nasdaq Global Select Market under the trading symbol “AVRO.”

Transfer Agent and Registrar

The transfer agent and registrar for our Common Stock is Computershare Trust Company, N.A. The transfer agent and registrar’s address is 250 Royall Street, Canton, Massachusetts 02021, and its telephone number is (800) 962-4284.

CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY [***], HAS BEEN OMITTED BECAUSE IT IS BOTH (I) NOT MATERIAL AND (II) WOULD LIKELY CAUSE COMPETITIVE HARM IF PUBLICLY DISCLOSED.

AMENDMENT NO. 1 TO LICENSE AGREEMENT

This AMENDMENT NO. 1 TO LICENSE AGREEMENT (herein referred to as "**Amendment No. 1**") is made and entered into as of this 21st day of February, 2018 (the "**Amendment No. 1 Effective Date**"), between BioMarin Pharmaceutical Inc., a Delaware corporation, with offices at 770 Lindaro Street, San Rafael, CA 94901 ("**BioMarin**"), and **AVROBIO, Inc.**, a Delaware corporation having a place of business at 700 Technology Square, Suite 101, Cambridge, MA 02139 ("**AVROBIO**"). Each of BioMarin and "AVROBIO" may be referred to herein as a "**Party**" or collectively as the "**Parties**."

1. This Amendment No. 1 shall serve as an amendment to that certain License Agreement, effective as of August 31, 2017 by and between AVROBIO and BioMarin (the "**Agreement**"). Except as expressly modified hereby, the Agreement shall continue in full force according to its terms. Capitalized terms not otherwise defined in this Amendment No. 1 shall have the meaning ascribed to such term in the Agreement.

2. Subject to the terms and conditions of the Agreement, including this Amendment No. 1, BioMarin agrees to supply AVROBIO with [***] in the amount set forth in Attachment 1 hereto.

3. Section 2.1 of the Agreement is hereby deleted and replaced with the following:

"**2.1 License Grants**.

2.1.1 Subject to the terms and conditions of this Agreement, BioMarin hereby grants to AVROBIO an exclusive, royalty-bearing license under the Licensed Patent Rights and Licensed Know-How to research, have researched, develop, have developed, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import, have imported, export and have exported Licensed Products in the Field in the Territory, including the right to grant sublicenses through multiple tiers, subject to any limitations on sublicensing expressly set forth in this Agreement (the "**License**").

2.1.2 Subject to the terms and conditions of this Agreement, BioMarin hereby grants to AVROBIO a limited, non-sublicensable, non-transferable, non-exclusive license to use [***] solely for the experiments set forth in <u>Schedule D</u>, which shall be performed by AVROBIO personnel at the facilities specified therein.

2.1.3 For clarity, except as set forth in Section 2.1.2, AVROBIO shall have no license rights either outside the Field or with respect to products other than Licensed Products. For further clarity, AVROBIO shall have no right to make or have made [***]."

4. The following Section 2.6 is hereby added to the Agreement:

"**2.6 Material Transfer ([***]).**

2.6.1 BioMarin agrees to supply AVROBIO with [***] in the amount set forth in <u>Schedule D</u> hereto.

2.6.2 AVROBIO will not use [***] in any activities or experiments other than in those experiments specifically set forth in <u>Schedule D</u>, which support AVROBIO's Development of Licensed Products. BioMarin shall at all times retain all right, title and interest in and to [***]. Except as otherwise provided in this Agreement, AVROBIO shall not, without the prior written consent of BioMarin, (a) reproduce or modify [***] or any portion thereof; (b) reverse assemble, reverse compile or reverse engineer [***], or otherwise attempt to discover any source code or underlying Confidential Information with respect to [***]; (c) rent, sell, lease, disclose or otherwise transfer or provide access to [***], or any derivative thereof, to another party; provided, that AVROBIO may allow access to [***] to its employees who require such access to conduct the experiments set forth in Schedule D and are bound by written agreements to retain and use [***] only in the manner permitted under this Agreement; or (d) alter, destroy, or otherwise remove any proprietary notices or labels on or supplied with [***].

2.6.3 AVROBIO acknowledges and agrees that [***] is experimental in nature and that [***] is provided "AS IS" and may not be functional. AVROBIO understands and agrees that [***] may have unpredictable and unknown biological and/or chemical properties, that [***] is to be handled and used with caution, and that [***] is not to be used for testing in or treatment of humans. [***] IS PROVIDED WITH NO WARRANTIES OF ANY KIND, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT IT IS FREE FROM THE RIGHTFUL CLAIM OF ANY THIRD PARTY, BY WAY OF INFRINGEMENT OR THE LIKE. FURTHER, BIOMARIN DISCLAIMS ANY REPRESENTATION OR WARRANTY THAT SAMPLES OF [***] PROVIDED HAVE NOT EXCEEDED THEIR EXPIRATION DATE(S).

2.6.4 In no event will BioMarin be liable for any use by AVROBIO of [***] or any loss, claim, damage or liability of any kind which may arise from or in connection with the use, handling or storage of [***] by or through AVROBIO. AVROBIO will indemnify BioMarin with respect to [***], as set forth in Article 9.

2.6.5 If AVROBIO conceives and/or reduces to practice inventions or discoveries, whether or not be patentable, in the course of using [***] that directly relate to [***] (and for clarity do not relate to AVROBIO's gene therapy Licensed Products ("**[***] Inventions**"), AVROBIO shall promptly and fully disclose to BioMarin any such [***] Inventions after the conception or reduction to practice thereof. AVROBIO hereby assigns all right, title, and interest in and to any [***] Inventions, including all intellectual property therein, to BioMarin, and AVROBIO shall obtain no rights, whether express or implied, in such [***] Inventions. AVROBIO agrees not to obtain or attempt to obtain patent coverage on [***] Inventions and agrees to execute such documents and perform such other acts, as BioMarin may reasonably request and at BioMarin's expense, to obtain, perfect and enforce BioMarin's rights in and to such [***] Inventions. AVROBIO hereby irrevocably designates and appoints BioMarin and its duly authorized officers and agents as AVROBIO's agent and attorney-in-fact to act for and on AVROBIO's behalf to execute, deliver and file any and all documents with the same legal force and effect as if executed by AVROBIO, if BioMarin is unable for any reason to secure AVROBIO's signature on any document needed in connection with the actions described in this Section 2.6.5. AVROBIO acknowledges that this appointment is coupled with an interest.

2.6.6 AVROBIO shall have and retain sole and exclusive ownership of all data created by AVROBIO's employees or independent contractors from the use of [***] pursuant to the terms and conditions of this Agreement. Reports regarding such work using [***] shall be provided in conjunction with the reports to be provided to BioMarin pursuant to Section 3.4 of this Agreement. AVROBIO shall have the right to publish or publicly present the results of the research conducted with [***] under this Agreement; provided, that BioMarin shall have the opportunity to review any such proposed manuscripts, non-confidential presentations, or other public disclosures describing said research. Any proposed publication or other non-confidential disclosure to third parties will be provided to BioMarin at least [***] days ([***] days in the case of abstracts) prior to the earlier of the date of submission to any journal for review or the date of publication or other disclosure. AVROBIO agrees to consider any of BioMarin's comments with respect to [***] that are provided within [***] days of BioMarin's receipt of the submitted documents and, at BioMarin's request, to delete any of BioMarin's Confidential Information contained therein. However, if submission of such manuscript for publication or delivery of such presentation or other disclosure would preclude BioMarin from obtaining patent protection for a [***] Invention(s) unless an application is filed with relevant patent authorities, AVROBIO shall, at its option, either delete the enabling portion of the proposed publication or presentation or withhold publication or delay presentation for an additional [***] days to permit BioMarin to prepare and file a patent application covering such [***] Invention(s).

2.6.7 Upon the completion of the experiments set forth in Schedule D, or any earlier expiration or termination of the Agreement, the license granted in Section 2.1.2 shall terminate and AVROBIO shall destroy (and will provide evidence documenting the manner of destruction to BioMarin) any remaining [***]."

5. The following sections are hereby added to Section 8.4.4 as additional sections that survive expiration or termination of the Agreement: Sections 2.6.4, 2.6.5, 2.6.6, and 2.6.7.

6. Section 9.2 is hereby deleted and replaced with the following:

"**9.2 Indemnification by AVROBIO.** AVROBIO will indemnify BioMarin, its Affiliates, and their respective directors, officers, employees, and agents ("**BioMarin Indemnitees**"), and defend and hold each of them harmless, from and against any and all Losses based on or suffered in connection with any Claims against any such BioMarin Indemnitee to the extent arising from or occurring as a result of or in connection with: (i) the Development and Commercialization of Licensed Products by or on behalf of AVROBIO, its Affiliates, and sublicensees, and each of their distributors, wholesalers, and agents, including, without limitation, Losses arising from Claims based on any theory of product liability (including actions in the form of tort, warranty or strict liability), (ii) the use, storage, or handling of [***] by or on behalf of AVROBIO (including its employees, independent contractors, and agents), (iii) any breach by AVROBIO, its Affiliates or sublicensees (including each of their respective directors, officers, employees, independent contractors, and agents) of this Agreement or of applicable law, (iv) the negligence or willful misconduct of AVROBIO, its Affiliates or sublicensees (including each of their respective directors, officers, employees, independent contractors, and agents); (v) breach of a contractual or fiduciary obligation owed by AVROBIO or its Affiliates or sublicensees to a Third Party (including misappropriation of trade secrets); or (vi) criminal investigations of, defense of criminal charges against, and criminal penalties levied on, AVROBIO or its Affiliates or sublicensees, or their respective directors, employees and agents; except, in each case, to the extent that such Losses arise out of or result from the gross negligence or willful misconduct of any BioMarin Indemnitee, or a breach by BioMarin of any provision of this Agreement..

7. Attachment 1 to this Amendment No. 1 is hereby added to the Agreement as Schedule D.

8. This Amendment No. 1 shall inure to the benefit of and be binding upon the Parties hereto and their respective heirs, successors, trustees, transferees and assigns.

9. This Amendment No. 1 may be executed in any number of counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the Parties hereto, intending to be legally bound hereby, have caused this Amendment No. 1 to be executed and delivered by their proper and duly authorized officers effective as of the day and year first above written.

BioMarin Pharmaceutical Inc.	**AVROBIO, Inc.**
/s/ Brinda Balakrishan	/s/ Geoff MacKay
By: Brinda Balakrishan	By: Geoff MacKay
Its: Group Vice President	Its: President & CEO

Attachment 1

Schedule D

[***]

CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY [***], HAS BEEN OMITTED BECAUSE IT IS BOTH (I) NOT MATERIAL AND (II) WOULD LIKELY CAUSE COMPETITIVE HARM IF PUBLICLY DISCLOSED.

AMENDMENT NO. 2 TO LICENSE AGREEMENT

This AMENDMENT NO. 2 TO LICENSE AGREEMENT (herein referred to as "**Amendment No. 2**") is made and entered into as of this 7th day of January, 2020 (the "**Amendment No. 2 Effective Date**"), between BioMarin Pharmaceutical Inc., a Delaware corporation, with offices at 770 Lindaro Street, San Rafael, CA 94901 ("**BioMarin**"), and **AVROBIO, Inc.**, a Delaware corporation having a place of business at One Kendall Square, Building 300, Suite 201, Cambridge, MA 02139 ("**AVROBIO**"). Each of BioMarin and "AVROBIO" may be referred to herein as a "**Party**" or collectively as the "**Parties**."

1. This Amendment No. 2 shall serve as an amendment to that certain License Agreement, effective as of August 31, 2017 and amended effective as of February 21, 2018 by and between AVROBIO and BioMarin (the "**Original Agreement**"). Except as expressly modified hereby, the Original Agreement shall continue in full force according to its terms. Capitalized terms not otherwise defined in this Amendment No. 2 shall have the meaning ascribed to such term in the Original Agreement.

2. AVROBIO's address set forth in the introductory paragraph of the Original Agreement and in Section 11.4 of the Original Agreement is hereby deleted in its entirety and replaced with the AVROBIO address set forth above in the introductory paragraph of this Amendment No. 2.

3. Section 2.1.2 of the Original Agreement is hereby deleted and replaced with the following:

   "2.1.2 Subject to the terms and conditions of this Agreement, BioMarin hereby grants to AVROBIO a limited, non-sublicensable, non-transferable, non-exclusive license to use [***] solely for the experiments set forth in <u>Schedule D</u>, which shall be performed by AVROBIO personnel or by a permitted Third Party at the facilities expressly specified therein. With BioMarin's prior written consent, AVROBIO may subcontract the performance of certain experiments set forth in <u>Schedule D</u> to additional Third Parties, including consultants. With respect to each and any such Third Party (a) such Third Party shall be bound by obligations consistent with AVROBIO's obligations set forth in Sections 2.6.2, 2.6.5, 2.6.7, and 7 of this Agreement; and (b) AVROBIO shall remain liable for such permitted Third Party's performance."

4. Section 2.6.1 of the Original Agreement is hereby deleted and replaced with the following:

   "2.6.1 BioMarin agrees to supply AVROBIO, and/or any permitted Third Party as directed by AVROBIO, with [***] in the amount set forth in <u>Schedule D</u> hereto."

5. As of the Amendment No. 2 Effective Date, <u>Schedule D</u> attached to the Original Agreement is replaced in its entirety with a new <u>Schedule D</u>, in the form attached to this Amendment No. 2 as **Attachment 1**.

6. This Amendment No. 2 shall inure to the benefit of and be binding upon the Parties hereto and their respective heirs, successors, trustees, transferees and assigns.

7. This Amendment No. 2 may be executed in any number of counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

[Signature page follows]

7.

IN WITNESS WHEREOF, the Parties hereto, intending to be legally bound hereby, have caused this Amendment No. 2 to be executed and delivered by their proper and duly authorized officers effective as of the day and year first above written.

BioMarin Pharmaceutical Inc.	**AVROBIO, Inc.**
/s/ Brinda Balakrishan	/s/ Geoff MacKay
By: Brinda Balakrishan	By: Geoff MacKay
Its: Group Vice President 08-Jan-2020	Its: CEO 08-Jan-2020

Attachment 1

Schedule D

[***]

AVROBIO, INC.

EMPLOYMENT AGREEMENT

This Employment Agreement ("Agreement") is made as of the 1st day of September, 2018, between AVROBIO, Inc., a Delaware corporation (the "Company"), and Deanna Petersen (the "Executive") and is effective as of the closing of the Company's first underwritten public offering of its equity securities pursuant to an effective registration statement under the Securities Act of 1933, as amended (the "Effective Date").

WHEREAS, the Company and the Executive are parties to an existing employment agreement, dated January 4, 2017 (the "Prior Agreement"); and

WHEREAS, the parties intend to replace the Prior Agreement with this Agreement, effective as of the Effective Date.

NOW, THEREFORE, in consideration of the mutual covenants and agreements herein contained and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties agree to restate the Prior Agreement as follows:

1. Employment.

(a) Term. The term of this Agreement shall commence on the Effective Date and continue until terminated in accordance with the provisions hereof (the "Term"). The Executive's employment with the Company will continue to be "at will," meaning that the Executive's employment may be terminated by the Company or the Executive at any time and for any reason subject to the terms of this Agreement.

(b) Position and Duties. During the Term, the Executive shall serve as the Chief Business Officer of the Company, and shall have supervision and control over and responsibility for the day-to-day business and affairs of the Company and shall have such other powers and duties as may from time to time be prescribed by the Board of Directors of the Company (the "Board"), the Chief Executive Officer of the Company (the "CEO") or other authorized executive. The Executive shall devote her full working time and efforts to the business and affairs of the Company. Notwithstanding the foregoing, the Executive may serve on other boards of directors, with the approval of the Board, or engage in religious, charitable or other community activities as long as such services and activities are disclosed to the Board and do not materially interfere with the Executive's performance of her duties to the Company as provided in this Agreement. For the avoidance of doubt, the Executive may continue to serve in the roles set forth on Schedule 1 hereto without the necessity of further approval from the Board, provided that no conflicts result in the future from the Executive's service in such role.

2. Compensation and Related Matters.

(a) Base Salary. During the Term, the Executive's annual base salary shall be $318,270. The Executive's base salary shall be reviewed annually by the Board or the Compensation Committee of the Board (the "Compensation Committee"). The base salary in effect at any given time is referred to herein as "Base Salary." The Base Salary shall be payable in a manner that is consistent with the Company's usual payroll practices for executive officers.

(b) Incentive Compensation. During the Term, the Executive shall be eligible to receive cash incentive compensation as determined by the Board or the Compensation Committee from time to time. The Executive's initial target annual incentive compensation shall be thirty-five percent of her Base Salary effective July 1, 2018 (resulting in a 30 percent effective rate for the 2018 target annual incentive compensation) (as in effect at any time, the "Target Annual Incentive Compensation"). Except as otherwise provided herein, to earn incentive compensation, the Executive must be employed by the Company on the day such incentive compensation is paid.

(c) Expenses. The Executive shall be entitled to receive prompt reimbursement for all reasonable expenses incurred by her during the Term in performing services hereunder, in accordance with the policies and procedures then in effect and established by the Company for its senior officers.

(d) Other Benefits. During the Term, the Executive shall be eligible to participate in or receive benefits under the Company's employee benefit plans in effect from time to time, subject to the terms of such plans. Additionally, during the Term, the Executive shall be eligible to receive such benefits and perquisites as those made available to the other employees of the Company generally.

(e) Vacations. During the Term, the Executive shall be entitled to paid vacation in accordance with the Company's policies and procedures, which shall be a minimum of 20 days in addition to the Company's paid holidays. The Executive shall also be entitled to all paid holidays given by the Company to its executive officers.

3. Termination. During the Term, the Executive's employment hereunder may be terminated without any breach of this Agreement under the following circumstances:

(a) Death. The Executive's employment hereunder shall terminate upon her death.

(b) Disability. The Company may terminate the Executive's employment if she is disabled and unable to perform the essential functions of the Executive's then existing position or positions under this Agreement with or without reasonable accommodation for a period of 180 days (which need not be consecutive) in any 12-month period. If any question shall arise as to whether during any period the Executive is disabled so as to be unable to perform the essential functions of the Executive's then existing position or positions with or without reasonable accommodation, the Executive may, and at the request of the Company shall, submit to the Company a certification in reasonable detail by a physician selected by the Company to whom the Executive or the Executive's guardian has no reasonable objection as to whether the Executive is so disabled or how long such disability is expected to continue, and such certification shall for the purposes of this Agreement be conclusive of the issue. The Executive shall cooperate with any reasonable request of the physician in connection with such certification. If such question shall arise and the Executive shall fail to submit such certification, the Company's determination of such issue shall be binding on the Executive. Nothing in this Section 3(b) shall be construed to waive the Executive's rights, if any, under existing law including, without limitation, the Family and Medical Leave Act of 1993, 29 U.S.C. §2601 *et seq*. and the Americans with Disabilities Act, 42 U.S.C. §12101 *et seq.*

(c) Termination by Company for Cause. The Company may terminate the Executive's employment hereunder for Cause. For purposes of this Agreement, "Cause" shall mean: (i) conduct by the Executive constituting a material act of misconduct in connection with the performance of her duties, including, without limitation, misappropriation of funds or property of the Company or any of its subsidiaries or affiliates other than the occasional, customary and de minimis use of Company property for personal purposes; (ii) the commission by the Executive of any felony or a misdemeanor involving moral turpitude, material deceit or dishonesty, or fraud, or any conduct by the Executive that would reasonably be expected to result in material injury or reputational harm to the Company or any of its subsidiaries or affiliates if she were retained in her position; (iii) continued non-performance by the Executive of her duties hereunder (other than by reason of the Executive's physical or mental illness, incapacity or disability) which has continued for more than 30 days following written notice (with a reasonably detailed summary of such alleged non-performance specified) of such non- performance from the Company's CEO or the Executive's direct supervisor; (iv) a breach by the Executive of any of the provisions incorporated into or contained in Section 7 of this Agreement; (v) a material violation by the Executive of the Company's written employment policies; or (vi) failure to cooperate with a bona fide internal investigation or an investigation by regulatory or law enforcement authorities, after being instructed by the Company to cooperate, or the willful destruction or failure to preserve documents or other materials known to be relevant to such investigation or the inducement of others to fail to cooperate or to produce documents or other materials in connection with such investigation.

(d) Termination Without Cause. The Company may terminate the Executive's employment hereunder at any time without Cause. Any termination by the Company of the Executive's employment under this Agreement which does not constitute a termination for Cause under Section 3(c) and does not result from the death or disability of the Executive under Section 3(a) or (b) shall be deemed a termination without Cause.

(e) Termination by the Executive. The Executive may terminate her employment hereunder at any time for any reason, including but not limited to Good Reason. For purposes of this Agreement, "Good Reason" shall mean that the Executive has complied with the "Good Reason Process" (hereinafter defined) following the occurrence of any of the following events: (i) a material diminution in the Executive's responsibilities, authority or duties; (ii) a material diminution in the Executive's Base Salary except for across-the-board salary reductions based on the Company's financial performance similarly affecting all or substantially all senior management employees of the Company; (iii) a material change in the geographic location at which the Executive provides services to the Company; or (iv) a material breach of this Agreement by the Company. "Good Reason Process" shall mean that (i) the Executive reasonably determines in good faith that a "Good Reason" condition has occurred; (ii) the Executive notifies the Company in writing of the first occurrence of the Good Reason condition within 60 days of the first occurrence of such condition; (iii) the Executive cooperates in good faith with the Company's efforts, for a period not less than 30 days following such notice (the "Cure Period"), to remedy the condition; (iv) notwithstanding such efforts, the Good Reason condition continues to exist; and (v) the Executive terminates her employment within 60 days after the end of the Cure Period. If the Company cures the Good Reason condition during the Cure Period, Good Reason shall be deemed not to have occurred.

(f) Notice of Termination. Except for termination as specified in Section 3(a), any termination of the Executive's employment by the Company or any such termination by the Executive shall be communicated by written Notice of Termination to the other party hereto. For purposes of this Agreement, a "Notice of Termination" shall mean a notice which shall indicate the specific termination provision in this Agreement relied upon.

(g) Date of Termination. "Date of Termination" shall mean: (i) if the Executive's employment is terminated by her death, the date of her death; (ii) if the Executive's employment is terminated on account of disability under Section 3(b) or by the Company for Cause under Section 3(c), the date on which Notice of Termination is given; (iii) if the Executive's employment is terminated by the Company under Section 3(d), the date on which a Notice of Termination is given; (iv) if the Executive's employment is terminated by the Executive under Section 3(e) without Good Reason, 30 days after the date on which a Notice of Termination is given, and (v) if the Executive's employment is terminated by the Executive under Section 3(e) with Good Reason, the date on which a Notice of Termination is given after the end of the Cure Period. Notwithstanding the foregoing, in the event that the Executive gives a Notice of Termination to the Company, the Company may unilaterally accelerate the Date of Termination and such acceleration shall not result in a termination by the Company for purposes of this Agreement.

4. Compensation Upon Termination.

(a) Termination Generally. If the Executive's employment with the Company is terminated for any reason, the Company shall pay or provide to the Executive (or to her authorized representative or estate) (i) any Base Salary earned through the Date of Termination, unpaid expense reimbursements (subject to, and in accordance with, Section 2(c) of this Agreement) and unused vacation that accrued through the Date of Termination on or before the time required by law but in no event more than 30 days after the Executive's Date of Termination; and (ii) any vested benefits the Executive may have under any employee benefit plan of the Company through the Date of Termination, which vested benefits shall be paid and/or provided in accordance with the terms of such employee benefit plans (collectively, the "Accrued Benefit").

(b) Termination by the Company Without Cause or by the Executive with Good Reason. During the Term, if the Executive's employment is terminated by the Company without Cause as provided in Section 3(d), or the Executive terminates her employment for Good Reason as provided in Section 3(e), then the Company shall pay the Executive her Accrued Benefit. In addition, subject to the Executive signing a separation agreement containing, among other provisions, a general release of claims in favor of the Company and related persons and entities, confidentiality, return of property and non-disparagement, in a form and manner satisfactory to the Company (the "Separation Agreement and Release") and the Separation Agreement and Release becoming irrevocable and fully effective and, if applicable, the Executive resigning as a member of the Board of Directors, all within 60 days after the Date of Termination (or such shorter time period provided in the Separation Agreement and Release):

(i) the Company shall pay the Executive an amount equal to 0.75 times the sum of the Executive's Base Salary (the "Severance Amount"). Notwithstanding the foregoing, if the Executive breaches any of the provisions incorporated into or contained in Section 7 of this Agreement, all payments of the Severance Amount shall immediately cease;

(ii) notwithstanding anything to the contrary in any applicable option agreement or stock-based award agreement, all time-based stock options and other time- based stock-based awards held by the Executive in which such stock option or other stock-based award would have vested if the Executive had remained employed for an additional nine months following the Date of Termination shall vest and become exercisable or nonforfeitable as of the Date of Termination;

(iii) if the Executive was participating in the Company's group health plan immediately prior to the Date of Termination and elects COBRA health continuation, then the Company shall pay to the Executive a monthly cash payment for nine months or the Executive's COBRA health continuation period, whichever ends earlier, in an amount equal to the monthly employer contribution that the Company would have made to provide health insurance to the Executive if the Executive had remained employed by the Company; and

(iv) the amounts payable under Section 4(b)(i) and (iii) shall be paid out in substantially equal installments in accordance with the Company's payroll practice over nine months commencing within 60 days after the Date of Termination; provided, however, that if the 60-day period begins in one calendar year and ends in a second calendar year, the Severance Amount shall begin to be paid in the second calendar year by the last day of such 60-day period; provided, further, that the initial payment shall include a catch-up payment to cover amounts retroactive to the day immediately following the Date of Termination. Each payment pursuant to this Agreement is intended to constitute a separate payment for purposes of Treasury Regulation Section 1.409A- 2(b)(2).

5. Change in Control Payment. The provisions of this Section 5 set forth certain terms of an agreement reached between the Executive and the Company regarding the Executive's rights and obligations upon the occurrence of a Change in Control of the Company. In the event of a Change in Control during the Term, all time-based stock options and other time- based stock-based awards held by the Executive as of the Effective Date that were granted to the Executive at least 12 months prior to the Effective Date shall immediately accelerate and become fully exercisable or nonforfeitable as of immediately prior to such Change in Control. These provisions are intended to assure and encourage in advance the Executive's continued attention and dedication to her assigned duties and her objectivity during the pendency and after the occurrence of any such event. These provisions shall apply in lieu of, and expressly supersede, the provisions of Section 4(b) regarding severance pay and benefits upon a termination of employment, if such termination of employment occurs within three months prior to or 18 months after the occurrence of the first event constituting a Change in Control. These provisions shall terminate and be of no further force or effect beginning 18 months after the occurrence of a Change in Control.

(a) Change in Control. During the Term, if within three months prior to or 18 months after a Change in Control, the Executive's employment is terminated by the Company without Cause as provided in Section 3(d) or the Executive terminates her employment for Good Reason as provided in Section 3(e), then, subject to the signing of the Separation Agreement and Release by the Executive and the Separation Agreement and Release becoming irrevocable and fully effective and, if applicable, the Executive resigning as a member of the Board of Directors, all within 60 days after the Date of Termination (or such shorter time period provided in the Separation Agreement and Release):

(i) the Company shall pay the Executive a lump sum in cash in an amount equal to one times the sum of (A) the Executive's current Base Salary (or the Executive's Base Salary in effect immediately prior to the Change in Control, if higher) and (B) the Executive's Target Annual Incentive Compensation then in effect;

(ii) notwithstanding anything to the contrary in any applicable option agreement or stock-based award agreement, all time-based stock options and other time- based stock-based awards held by the Executive shall immediately accelerate and become fully exercisable or nonforfeitable as of the Date of Termination;

(iii) if the Executive was participating in the Company's group health plan immediately prior to the Date of Termination and elects COBRA health continuation, then the Company shall pay to the Executive a monthly cash payment for twelve months or the Executive's COBRA health continuation period, whichever ends earlier, in an amount equal to the monthly employer contribution that the Company would have made to provide health insurance to the Executive if the Executive had remained employed by the Company; and

(iv) The amounts payable under Section 5(a)(i) and (iii) shall be paid or commence to be paid within 60 days after the Date of Termination; provided, however, that if the 60-day period begins in one calendar year and ends in a second calendar year, such payment shall be paid or commence to be paid in the second calendar year by the last day of such 60-day period.

(b) Additional Limitation.

(i) Anything in this Agreement to the contrary notwithstanding, in the event that the amount of any compensation, payment or distribution by the Company to or for the benefit of the Executive, whether paid or payable or distributed or distributable pursuant to the terms of this Agreement or otherwise, calculated in a manner consistent with Section 280G of the Internal Revenue Code of 1986, as amended (the "Code") and the applicable regulations thereunder (the "Aggregate Payments"), would be subject to the excise tax imposed by Section 4999 of the Code, then the Aggregate Payments shall be reduced (but not below zero) so that the sum of all of the Aggregate Payments shall be $1.00 less than the amount at which the Executive becomes subject to the excise tax imposed by Section 4999 of the Code; provided that such reduction shall only occur if it would result in the Executive receiving a higher After Tax Amount (as defined below) than the Executive would receive if the Aggregate Payments were not subject to such reduction. In such event, the Aggregate Payments shall be reduced in the following order, in each case, in reverse chronological order beginning with the Aggregate Payments that are to be paid the furthest in time from consummation of the transaction that is subject to Section 280G of the Code: (1) cash payments not subject to Section 409A of the Code; (2) cash payments subject to Section 409A of the Code; (3) equity- based payments and acceleration; and (4) non-cash forms of benefits; provided that in the case of all the foregoing Aggregate Payments all amounts or payments that are not subject to calculation under Treas. Reg. §1.280G-1, Q&A-24(b) or (c) shall be reduced before any amounts that are subject to calculation under Treas. Reg. §1.280G-1, Q&A- 24(b) or (c).

(ii) For purposes of this Section 5(b), the "After Tax Amount" means the amount of the Aggregate Payments less all federal, state, and local income, excise and employment taxes imposed on the Executive as a result of the Executive's receipt of the Aggregate Payments. For purposes of determining the After Tax Amount, the Executive shall be deemed to pay federal income taxes at the highest marginal rate of federal income taxation applicable to individuals for the calendar year in which the determination is to be made, and state and local income taxes at the highest marginal rates of individual taxation in each applicable state and locality, net of the maximum reduction in federal income taxes which could be obtained from deduction of such state and local taxes.

(iii) The determination as to whether a reduction in the Aggregate Payments shall be made pursuant to Section 5(b)(i) shall be made by a nationally recognized accounting firm selected by the Company (the "Accounting Firm"), which shall provide detailed supporting calculations both to the Company and the Executive within 15 business days of the Date of Termination, if applicable, or at such earlier time as is reasonably requested by the Company or the Executive. Any determination by the Accounting Firm shall be binding upon the Company and the Executive.

(c) Definitions. For purposes of this Section 5, the following terms shall have the following meanings:

"Change in Control" shall mean any of the following:

(i) any "person," as such term is used in Sections 13(d) and 14(d) of the Securities Exchange Act of 1934, as amended (the "Act") (other than the Company, any of its subsidiaries, or any trustee, fiduciary or other person or entity holding securities under any employee benefit plan or trust of the Company or any of its subsidiaries), together with all "affiliates" and "associates" (as such terms are defined in Rule 12b-2 under the Act) of such person, shall become the "beneficial owner" (as such term is defined in Rule 13d-3 under the Act), directly or indirectly, of securities of the Company representing 50 percent or more of the combined voting power of the Company's then outstanding securities having the right to vote in an election of the Board ("Voting Securities") (in such case other than as a result of an acquisition of securities directly from the Company); or

(ii) the date a majority of the members of the Board is replaced during any 12-month period by directors whose appointment or election is not endorsed by a majority of the members of the Board before the date of the appointment or election; or

(iii) the consummation of (A) any consolidation or merger of the Company where the stockholders of the Company, immediately prior to the consolidation or merger, would not, immediately after the consolidation or merger, beneficially own (as such term is defined in Rule 13d-3 under the Act), directly or indirectly, shares representing in the aggregate more than 50 percent of the voting shares of the Company issuing cash or securities in the consolidation or merger (or of its ultimate parent corporation, if any), or (B) any sale or other transfer (in one transaction or a series of transactions contemplated or arranged by any party as a single plan) of all or substantially all of the assets of the Company.

Notwithstanding the foregoing, a "Change in Control" shall not be deemed to have occurred for purposes of the foregoing clause (i) solely as the result of an acquisition of securities by the Company which, by reducing the number of shares of Voting Securities outstanding, increases the proportionate number of Voting Securities beneficially owned by any person to 50 percent or more of the combined voting power of all of the then outstanding Voting Securities; provided, however, that if any person referred to in this sentence shall thereafter become the beneficial owner of any additional shares of Voting Securities (other than pursuant to a stock split, stock dividend, or similar transaction or as a result of an acquisition of securities directly from the Company) and immediately thereafter beneficially owns 50 percent or more of the combined voting power of all of the then outstanding Voting Securities, then a "Change in Control" shall be deemed to have occurred for purposes of the foregoing clause (i).

6. Section 409A.

(a) Anything in this Agreement to the contrary notwithstanding, if at the time of the Executive's separation from service within the meaning of Section 409A of the Code, the Company determines that the Executive is a "specified employee" within the meaning of Section 409A(a)(2)(B)(i) of the Code, then to the extent any payment or benefit that the Executive becomes entitled to under this Agreement on account of the Executive's separation from service would be considered deferred compensation otherwise subject to the 20 percent additional tax imposed pursuant to Section 409A(a) of the Code as a result of the application of Section 409A(a)(2)(B)(i) of the Code, such payment shall not be payable and such benefit shall not be provided until the date that is the earlier of (A) six months and one day after the Executive's separation from service, or (B) the Executive's death. If any such delayed cash payment is otherwise payable on an installment basis, the first payment shall include a catch-up payment covering amounts that would otherwise have been paid during the six-month period but for the application of this provision, and the balance of the installments shall be payable in accordance with their original schedule.

(b) All in-kind benefits provided and expenses eligible for reimbursement under this Agreement shall be provided by the Company or incurred by the Executive during the time periods set forth in this Agreement. All reimbursements shall be paid as soon as administratively practicable, but in no event shall any reimbursement be paid after the last day of the taxable year following the taxable year in which the expense was incurred. The amount of in-kind benefits provided or reimbursable expenses incurred in one taxable year shall not affect the in-kind benefits to be provided or the expenses eligible for reimbursement in any other taxable year (except for any lifetime or other aggregate limitation applicable to medical expenses). Such right to reimbursement or in-kind benefits is not subject to liquidation or exchange for another benefit.

(c) To the extent that any payment or benefit described in this Agreement constitutes "non-qualified deferred compensation" under Section 409A of the Code, and to the extent that such payment or benefit is payable upon the Executive's termination of employment, then such payments or benefits shall be payable only upon the Executive's "separation from service." The determination of whether and when a separation from service has occurred shall be made in accordance with the presumptions set forth in Treasury Regulation Section 1.409A-1(h).

(d) The parties intend that this Agreement will be administered in accordance with Section 409A of the Code. To the extent that any provision of this Agreement is ambiguous as to its compliance with Section 409A of the Code, the provision shall be read in such a manner so that all payments hereunder comply with Section 409A of the Code. Each payment pursuant to this Agreement is intended to constitute a separate payment for purposes of Treasury Regulation Section 1.409A-2(b)(2). The parties agree that this Agreement may be amended, as reasonably requested by either party, and as may be necessary to fully comply with Section 409A of the Code and all related rules and regulations in order to preserve the payments and benefits provided hereunder without additional cost to either party.

(e) The Company makes no representation or warranty and shall have no liability to the Executive or any other person if any provisions of this Agreement are determined to constitute deferred compensation subject to Section 409A of the Code but do not satisfy an exemption from, or the conditions of, such Section.

7. Confidential Information, Noncompetition and Cooperation.

(a) The terms of the Confidentiality and IP Assignment Agreement (the "Restrictive Covenant Agreement"), between the Company and the Executive, attached hereto as Exhibit A, shall continue to be in full force and effect and are incorporated by reference in this Agreement. The Executive hereby reaffirms the terms of the Restrictive Covenant Agreement as material terms of this Agreement.

(b) Third-Party Agreements and Rights. The Executive hereby confirms that the Executive is not bound by the terms of any agreement with any previous employer or other party which restricts in any way the Executive's use or disclosure of information or the Executive's engagement in any business. The Executive represents to the Company that the Executive's execution of this Agreement, the Executive's employment with the Company and the performance of the Executive's proposed duties for the Company will not violate any obligations the Executive may have to any such previous employer or other party. In the Executive's work for the Company, the Executive will not disclose or make use of any information in violation of any agreements with or rights of any such previous employer or other party, and the Executive will not bring to the premises of the Company any copies or other tangible embodiments of non-public information belonging to or obtained from any such previous employment or other party.

(c) Litigation and Regulatory Cooperation. During and after the Executive's employment, the Executive shall reasonably cooperate with the Company in the defense or prosecution of any claims or actions now in existence or which may be brought in the future against or on behalf of the Company which relate to events or occurrences that transpired while the Executive was employed by the Company. The Executive's full cooperation in connection with such claims or actions shall include, but not be limited to, being available to meet with counsel to prepare for discovery or trial and to act as a witness on behalf of the Company at mutually convenient times, taking into consideration Executive's then current business and personal commitments. During and after the Executive's employment, the Executive also shall cooperate fully with the Company in connection with any investigation or review of any federal, state or local regulatory authority as any such investigation or review relates to events or occurrences that transpired while the Executive was employed by the Company. The Company shall reimburse the Executive for any reasonable out-of-pocket expenses incurred in connection with the Executive's performance of obligations pursuant to this Section 7(c).

(d) Relief. The Executive agrees that it would be difficult to measure any damages caused to the Company which might result from any breach by the Executive of the promises incorporated into or set forth in this Section 7, and that in any event money damages would be an inadequate remedy for any such breach. Accordingly, subject to Section 8 of this Agreement, the Executive agrees that if the Executive breaches, or proposes to breach, any portion of this Agreement, the Company shall be entitled, in addition to all other remedies that it may have, to an injunction or other appropriate equitable relief to restrain any such breach without showing or proving any actual damage to the Company. In addition, in the event the Executive breaches this Section 7 or the provisions incorporated herein during a period when she is receiving severance payments pursuant to Section 4 or Section 5 hereof, the Company shall have the right to suspend or terminate such severance payments. Such suspension or termination shall not limit the Company's other options with respect to relief for such breach and shall not relieve the Executive of her duties under this Agreement.

(e) Protected Disclosures and Other Protected Action. Nothing contained in this Agreement limits the Executive's ability to communicate with any federal, state or local governmental agency or commission, including to provide documents or other information, without notice to the Company.

8. Arbitration of Disputes. Any controversy or claim arising out of or relating to this Agreement or the breach thereof or otherwise arising out of the Executive's employment or the termination of that employment (including, without limitation, any claims of unlawful employment discrimination whether based on age or otherwise) shall, to the fullest extent permitted by law, be settled by arbitration in any forum and form agreed upon by the parties or, in the absence of such an agreement, under the auspices of the American Arbitration Association ("AAA") in Boston, Massachusetts in accordance with the Employment Dispute Resolution Rules of the AAA, including, but not limited to, the rules and procedures applicable to the selection of arbitrators. In the event that any person or entity other than the Executive or the Company may be a party with regard to any such controversy or claim, such controversy or claim shall be submitted to arbitration subject to such other person or entity's agreement. Judgment upon the award rendered by the arbitrator may be entered in any court having jurisdiction thereof. This Section 8 shall be specifically enforceable. Notwithstanding the foregoing, this Section 8 shall not preclude either party from pursuing a court action for the sole purpose of obtaining a temporary restraining order or a preliminary injunction in circumstances in which such relief is appropriate; provided that any other relief shall be pursued through an arbitration proceeding pursuant to this Section 8.

9. Consent to Jurisdiction. To the extent that any court action is permitted consistent with or to enforce Section 8 of this Agreement, the parties hereby consent to the jurisdiction of the Superior Court of the Commonwealth of Massachusetts and the United States District Court for the District of Massachusetts. Accordingly, with respect to any such court action, the Executive (a) submits to the personal jurisdiction of such courts; (b) consents to service of process; and (c) waives any other requirement (whether imposed by statute, rule of court, or otherwise) with respect to personal jurisdiction or service of process.

10. Integration. This Agreement and the Restrictive Covenant Agreement constitute the entire agreement between the parties with respect to the subject matter hereof and supersede all prior agreements between the parties concerning such subject matter, including the Prior Agreement.

11. Withholding. All payments made by the Company to the Executive under this Agreement shall be net of any tax or other amounts required to be withheld by the Company under applicable law.

12. Successor to the Executive. This Agreement shall inure to the benefit of and be enforceable by the Executive's personal representatives, executors, administrators, heirs, distributees, devisees and legatees. In the event of the Executive's death after her termination of employment but prior to the completion by the Company of all payments due to her under this Agreement, the Company shall continue such payments to the Executive's beneficiary designated in writing to the Company prior to her death (or to her estate, if the Executive fails to make such designation).

13. Enforceability. If any portion or provision of this Agreement (including, without limitation, any portion or provision of any section of this Agreement) shall to any extent be declared illegal or unenforceable by a court of competent jurisdiction, then the remainder of this Agreement, or the application of such portion or provision in circumstances other than those as to which it is so declared illegal or unenforceable, shall not be affected thereby, and each portion and provision of this Agreement shall be valid and enforceable to the fullest extent permitted by law.

14. Survival. The provisions of this Agreement shall survive the termination of this Agreement and/or the termination of the Executive's employment to the extent necessary to effectuate the terms contained herein.

15. Waiver. No waiver of any provision hereof shall be effective unless made in writing and signed by the waiving party. The failure of any party to require the performance of any term or obligation of this Agreement, or the waiver by any party of any breach of this Agreement, shall not prevent any subsequent enforcement of such term or obligation or be deemed a waiver of any subsequent breach.

16. Notices. Any notices, requests, demands and other communications provided for by this Agreement shall be sufficient if in writing and delivered in person or sent by a nationally recognized overnight courier service or by registered or certified mail, postage prepaid, return receipt requested, to the Executive at the last address the Executive has filed in writing with the Company or, in the case of the Company, at its main offices, attention of the Board.

17. Amendment. This Agreement may be amended or modified only by a written instrument signed by the Executive and by a duly authorized representative of the Company.

18. Governing Law. This is a Massachusetts contract and shall be construed under and be governed in all respects by the laws of the Commonwealth of Massachusetts, without giving effect to the conflict of laws principles thereof.

19. Counterparts. This Agreement may be executed in any number of counterparts, each of which when so executed and delivered shall be taken to be an original; but such counterparts shall together constitute one and the same document.

20. Successor to Company. The Company shall require any successor (whether direct or indirect, by purchase, merger, consolidation or otherwise) to all or substantially all of the business or assets of the Company expressly to assume and agree to perform this Agreement to the same extent that the Company would be required to perform it if no succession had taken place. Failure of the Company to obtain an assumption of this Agreement at or prior to the effectiveness of any succession shall be a material breach of this Agreement.

21. Gender Neutral. Wherever used herein, a pronoun in the masculine or feminine gender shall be considered as including the opposite gender as well unless the context clearly indicates otherwise.

IN WITNESS WHEREOF, the parties have executed this Agreement effective on the date and year first above written.

AVROBIO, INC.

By:	/s/ Geoff MacKay
Name:	Geoff MacKay
Title:	Chief Executive Officer

EXECUTIVE

/s/ Deanna M. Petersen

Deanna Petersen

Schedule 1

Approved Activities

Board Member, Tecogen, Inc. (TGEN)

Exhibit A

Confidentiality and IP Assignment Agreement

Exhibit 21.1

List of Subsidiaries

Subsidiary	Jurisdiction of incorporation or organization
AVROBIO Inc.	Ontario, Canada
AVROBIO Australia Pty Ltd	Australia
AVROBIO Securities Corporation	Massachusetts

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-8 No. 333-225788) pertaining to the AVROBIO, Inc. Amended and Restated 2015 Stock Option and Grant Plan, the AVROBIO, Inc. 2018 Stock Option and Incentive Plan, and the AVROBIO, Inc. 2018 Employee Stock Purchase Plan,

(2) Registration Statement (Form S-8 No. 333-230493) pertaining to the Inducement Stock Option Agreement of AVROBIO, Inc.,

(3) Registration Statement (Form S-8 No. 333-230494) pertaining to the AVROBIO, Inc. 2018 Stock Option and Incentive Plan and the AVROBIO, Inc. 2018 Employee Stock Purchase Plan,

(4) Registration Statement (Form S-3 No. 333-232489) of AVROBIO, Inc.,

(5) Registration Statement (Form S-8 No. 333-234641) pertaining to the Inducement Stock Option Agreement of AVROBIO, Inc.,

(6) Registration Statement (Form S-3 No. 333-235641) of AVROBIO, Inc., and

(7) Registration Statement (Form S-8 No. 333-235643) pertaining to the AVROBIO, Inc. 2019 Inducement Plan and the Inducement Stock Option Agreement of AVROBIO, Inc.;

of our report dated March 16, 2020, with respect to the consolidated financial statements of AVROBIO, Inc. included in this Annual Report (Form 10-K) of AVROBIO, Inc. for the year ended December 31, 2019.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 16, 2020

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Geoff MacKay, certify that:

1. I have reviewed this Annual Report on Form 10-K of AVROBIO, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2020

By: /s/ Geoff MacKay

Geoff MacKay
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Erik Ostrowski, certify that:

1. I have reviewed this Annual Report on Form 10-K of AVROBIO, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting

Date: March 16, 2020

By: /s/ Erik Ostrowski
Erik Ostrowski
Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of AVROBIO, Inc. (the “Company”) on Form 10-K for the year ended December 31, 2019 as filed with the Securities and Exchange Commission on the date hereof (the “Report”), each of the undersigned officers of the Company certifies, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, to the best of his or her knowledge that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 16, 2020	By:	/s/ Geoff MacKay **Geoff MacKay** **Chief Executive Officer** **(Principal Executive Officer)**
Date: March 16, 2020	By:	/s/ Erik Ostrowski **Erik Ostrowski** **Chief Financial Officer** **(Principal Financial Officer)**